ORIGINAL ARTICLE

Telacebec, a Potent Agent in the Fight against Tuberculosis
Findings from a Randomized, Phase 2 Clinical Trial and Beyond

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Abstract

Rationale: Antibiotic-resistant mycobacterial infections are a major threat to health care. Telacebec is a novel, first-in-class agent targeting mycobacterial cellular energy production in a range of pathogenic mycobacteria, including *Mycobacterium tuberculosis*, *M. leprae*, and *M. ulcerans*.

Objectives: To explore telacebec's early bactericidal activity, tolerability, safety, and pharmacokinetics in patients with pulmonary tuberculosis and to summarize its current state of development for other diseases.

Methods: We randomly assigned 64 patients with smear-positive, drug-sensitive tuberculosis to daily telacebec 100, 200, or 300 mg, or standard four-drug treatment as control, for 14 days.

Measurements and Main Results: Sputum collected overnight was cultured in liquid and on solid media to determine the change of viable mycobacteria over time. Safety and tolerability were assessed daily. A full pharmacokinetic profile was obtained on Day 14. We found a dose-dependent reduction of the sputum mycobacterial load with a mean ± SD daily change for telacebec 300 mg and control, respectively, of 0.097 ± 0.050 and 0.200 ± 0.073 log colony-forming units, and 3.738 ± 2.747 and 6.853 ± 1.194 hours to culture positivity over the first 14 days of treatment. Pharmacokinetics were dose proportional. Telacebec was well tolerated and safe, with low adverse event rates across all doses.

Conclusions: These results confirm telacebec's clinical activity against *M. tuberculosis*. Longer trials, in combination with other agents, are required to validate these results and to investigate telacebec's full potential. These results encourage the exploration of telacebec for more effective, shorter treatment regimens for leprosy and Buruli ulcer. A clinical trial for Buruli ulcer is under way.

Clinical trial registered with URL (NCT 03563599).

Keywords: tuberculosis; leprosy; Buruli ulcer; treatment

Tuberculosis (TB) remains the major infectious cause of death, and with 10.6 million individuals developing active TB and 1.5 million deaths in 2021, we are far from targets to end TB (1, 2). With half a million cases resistant to at least the cornerstone first-line drugs isoniazid and rifampin and only one-third of patients accessing TB care, drug-resistant TB (DR-TB) is a public health crisis in many countries. It has been estimated that 85% of households affected by DR-TB face catastrophic costs (1).

There has been considerable progress in DR-TB treatment in recent years. Bedaquiline (BDQ) and delamanid were the first new drugs approved for the treatment of patients with DR-TB after nearly four decades, followed a few years later by pretomanid (3, 4). New regimens currently rolled out are based on the combination of BDQ, pretomanid, and linezolid. These all-oral regimens with a duration of 6 months (5, 6) are a marked improvement for many patients with TB who cannot receive first-line treatment, but they are still no shorter than the lengthy standard treatment course, resistance rates to the new agents are rising (7, 8), and guidelines for special groups such as pregnant women and children

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This article has a related editorial.

A data supplement for this article is available via the Supplements tab at the top of the online article.

Artificial Intelligence Disclaimer: No artificial intelligence tools were used in writing this manuscript.

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At a Glance Commentary

Scientific Knowledge on the Subject: Telacebec is a new first-in-class antituberculosis drug that targets mycobacterial energy production. Preliminary results of a phase IIa proof-of-concept study showed bactericidal activity, with an increase in time to positivity of liquid overnight sputum cultures of patients with pulmonary tuberculosis.

What This Study Adds to the Field: Comprehensive results of the phase IIa proof-of-concept clinical trial in patients with pulmonary TB confirm telacebec as a first-in-class agent with clinical activity against *Mycobacterium tuberculosis*, with dose-proportional pharmacokinetics. The drug was well tolerated and safe.

are lacking. It is clear that more novel drugs are needed to further shorten treatment duration and increase regimen safety.

Telacebec is a new first-in-class anti-TB drug that targets mycobacterial energy production. Its target, the QcrB subunit of the cytochrome bc1 complex, has no known human homolog (Figure 1) (9). *In vitro*, telacebec is active at low concentrations against replicating mycobacteria. There is low potential for *in vivo* drug–drug interactions because of induction or inhibition of cytochrome P450 and the efflux transporter P-glycoprotein (9). Telacebec inhibits *Mycobacterium tuberculosis* H37Rv growth (minimum inhibitory concentration required to inhibit the growth of 50% of organisms [MIC_{50}]) at a low concentration of 2.7 nM in culture broth medium and at 0.28 nM inside macrophages. This strong inhibitory potential is conserved in most clinical wild-type or DR-TB isolates (9).

A phase Ia, single-dose ascending study showed a favorable safety and pharmacokinetic (PK) profile up to 800 mg/d, supporting once-daily dosing (10). Food increased plasma concentrations of telacebec, and the terminal half-life was remarkably long. A phase Ib multiple-dose ascending study ranging from 20 to 320 mg/d over 14 days (11) showed no safety concerns. A maximum dose of 300 mg/d was chosen because exposures correlated with treatment effect in animal studies and steady state was reached at 12 days with no further drug accumulation (11).

We present comprehensive results of a phase IIa proof-of-concept clinical trial in patients with pulmonary TB, of which topline results were previously published in letter format (12). We also discuss the potential of telacebec for neglected but clinically important atypical mycobacterial infections, as well as novel combination regimens for better TB treatments.

Methods

See the data supplement for details, including murine studies.

Participants

From July 2018 to September 2019, two centers in South Africa (TASK, in Bellville, and the University of Cape Town Lung Institute, in Cape Town) recruited treatment-naive participants with at least one episode of smear-positive (13), rifampin-sensitive, and radiologically confirmed pulmonary TB who were between 18 and 75 years of age, had a body weight of 35–100 kg, and were able to produce at least 10 ml sputum during a 16-hour collection period. Excluded were patients with poor general condition or clinically extensive TB, diabetes mellitus, HIV infection with a CD4 cell count of <250 cells/L, and other conditions making participation unsafe or interfering with the interpretation of the measurements.

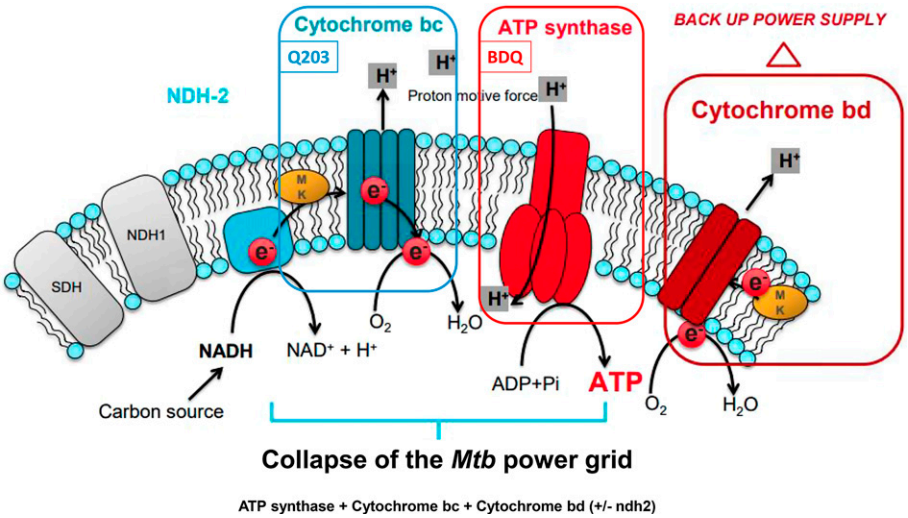

Figure 1. Telacebec (Q203) and bedaquiline (BDQ) target distinct mechanisms of the energy production of *Mycobacterium tuberculosis* (*Mtb*). The figure illustrates the oxidative phosphorylation in *Mtb* and target sites of Q203 and BDQ. Electrons derived from NADH are fed into the electron transport chain by NADH dehydrogenase leading to the reduction of the menaquinone pool (MK). From the MK pool, electrons can be transferred to the cytochrome bc1 complex which transfers the electrons onto oxygen. Alternatively, oxygen can be reduced by a cytochrome bd-type terminal oxidase, which directly accepts electrons from the menaquinone pool. During electron transport along the respiratory chain, protons are pumped across the membrane, leading to a proton motive force, of which the energy can be used by ATP synthase for synthesis of ATP. Combining BDQ and Q203 may increase pressure on mycobacteria potentially leading to a synergistic effect. *M. ulcerans* and *M. leprae* lack cytochrome bd, rendering these mycobacteria highly susceptible to Q203. Figure courtesy of Dr. Anil Koul, Johnson & Johnson, Beerse, Belgium. NAD = nicotinamide adenine dinucleotide; Pi = inorganic phosphate; SDH = succinate dehydrogenase; type 1 and type 2 = NADH dehydrogenase (NDH1 and NDH2).

The study received local ethics and regulatory approvals and is registered at ClinicalTrials.gov (NCT 03563599).

Randomization and Treatment

Eligible participants were randomly assigned 5:5:5:3 to one of four parallel treatment arms to receive either telacebec at doses of 100, 200 or 300 mg or weight-adjusted standard of care (SOC; supplied as Rifafour e-275) orally once daily for 14 days. This smaller group served as control for the quantitative mycobacteriology. Randomization occurred through a central interactive voice response system (Cenduit LLC). Upon treatment completion or early withdrawal, all participants were referred to local community TB clinics to be started on SOC treatment.

Safety and Tolerability

Patients were inpatients from screening until 24 hours after the last study drug administration. Adverse events (AEs) were collected from the time of first drug administration until the final follow-up visit 21 days later. Physical examinations, vital signs, safety laboratory testing (chemistry, hematology, urinalysis, and coagulation), and ECGs were assessed at predetermined time points throughout the study. AEs were reported according to the Medical Dictionary for Regulatory Activities version 19.1.

Microbiology and PK Profile

For screening, spot sputa were collected and ssessed for the presence and quantity of acid-fast bacilli (using the auramine O staining method) as well as genetic resistance to rifampin (GenoType MTBDRplus; Hain Lifesciences). Serial 16-hour overnight sputa were collected from 2 days before treatment start up to Day 14, cultured in Mycobacteria Growth Indicator Tube with time-to-positivity (TTP) assessments, and colony-forming unit (cfu) counts. Early bactericidal activity (EBA) on TTP assessment (EBA_{TTP}), the primary study endpoint, was reported as the change in TTP from baseline over time measured in hours, and EBA according to cfu count (EBA_{cfu}) as the change in log_{10}(cfu) over time per milliliter of sputum. Intense PK measurements of plasma and urine were performed at Days 1 and 14; trough concentrations were measured at Days 4, 6, 8, 10, and 12 (*see* the data supplement for detailed methods).

Statistical Analysis

This was a phase IIa, open-label, randomized study. The sample of 15 patients per telacebec dose was aligned with similar studies of this kind. EBA_{TTP}(0–14), EBA_{TTP}(0–2), and EBA_{TTP}(2–14) and EBA_{cfu}(0–14), EBA_{cfu}(0–2), and EBA_{cfu}(2–14) were described with at most three parameters from an appropriate function of log(TTP) or log(cfu) on time, respectively. Analysis populations were per protocol (PPROT), which included only subjects strictly without procedural deviations, and modified intention-to-treat (mITT), which was defined as every participant who completed study treatment. EBA and PK analyses were done primarily on the PPROT population and repeated on the mITT population, whereas the mITT population was used for safety analyses. The preclinically determined MIC_{50} of 2.7 nM was used as part of the PK/pharmacodynamic analyses. Nonlinear regression modeling was used to determine the rate of change of log_{10}(TTP) and

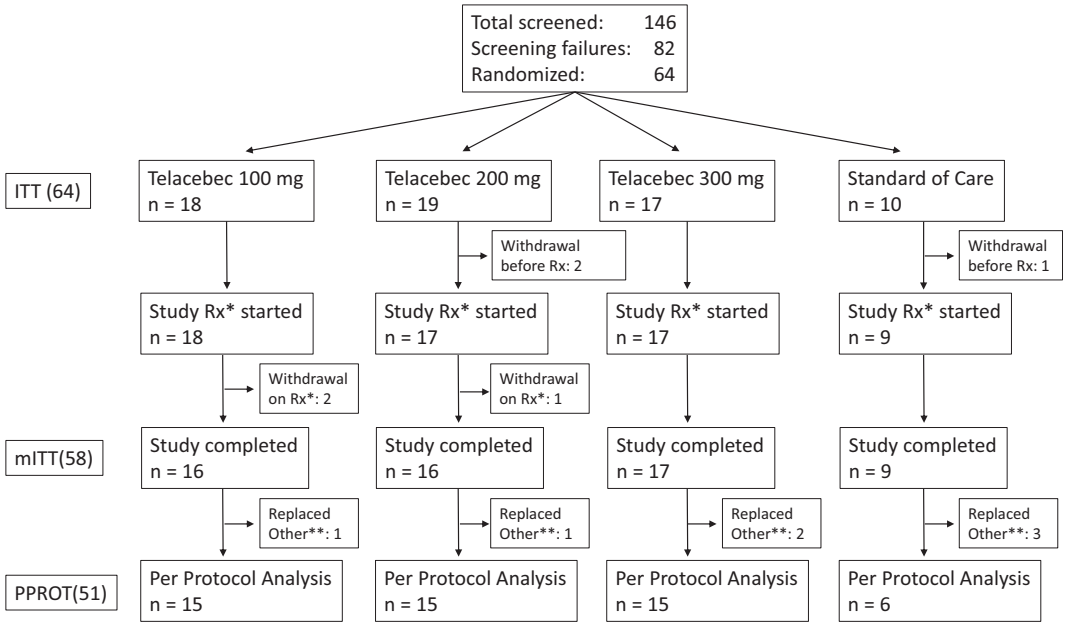

Figure 2. Overview of the study population. Flow diagram showing an overview of the study population. Of the three participants who were withdrawn on study treatment (Rx), one was withdrawn because of worsening TB, one withdrew after a single dose (both in the telacebec 100 mg group), and one was withdrawn because he had withheld information about a previous recent TB episode (in the telacebec 200 mg group). One participant had an episode of hemoptysis before the initiation of Rx. Seven participants were replaced after they had completed Rx because of insufficient volumes of baseline sputum samples and one because of the use of prohibited medication (steroids). These participants were included in the mITT but not the PPROT population. ITT = intention to treat; mITT = modified intention to treat; PPROT = per protocol.
*Treatment (Rx).
**Seven participants were replaced after they had completed study treatment because of insufficient volumes of baseline sputum samples and one because of the use of prohibited medication (steroids).

Table 1. Participant Characteristics at Baseline

	Statistic	100 mg ($n=18$)	200 mg ($n=19$)	300 mg ($n=17$)	SOC ($n=10$)	Total ($N=64$)
Baseline characteristics (intent to treat population)						
Age, yr	Mean (SD)	35.1 (9.73)	31.1 (10.95)	31.0 (9.46)	28.0 (8.39)	31.7 (9.92)
Female	*n* (%)	6 (33.3)	6 (31.6)	1 (5.9)	3 (30.0)	16 (25.0)
Male	*n* (%)	12 (66.7)	13 (68.4)	16 (94.1)	7 (70.0)	48 (75.0)
Race						
Black or African American	*n* (%)	9 (50.0)	10 (52.6)	9 (52.9)	4 (40.0)	32 (50.0)
Mixed race	*n* (%)	9 (50.0)	9 (47.4)	8 (47.1)	6 (60.0)	32 (50.0)
HIV status						
Positive	*n* (%)	1 (5.6)	4 (21.1)	4 (23.5)	0	9 (14.1)
Negative	*n* (%)	17 (94.4)	13 (68.4)	13 (76.5)	9 (90.0)	52 (81.3)
Missing	*n* (%)	0	2 (10.5)	0	1 (10.0)	3 (4.7)
BMI, kg/m^2	Mean (SD)	19.5 (3.28)	19.0 (3.26)	18.8 (2.14)	18.6 (1.34)	19.1 (2.73)
Extent of disease (per protocol population)		($n=15$)	($n=15$)	($n=15$)	($n=6$)	($n=51$)
Sputum mycobacterial load						
Liquid media (time to positivity, h)	Mean (SD)	119 (52)	123 (37)	113 (44)	134 (31)	120 (43)
Solid media (log colony-forming units)	Mean (SD)	5.98 (1.67)	6.34 (0.99)	6.78 (0.88)	6.27 (0.69)	6.36 (1.19)
Radiology scores		($n=14$)	($n=13$)	($n=15$)	($n=6$)	($n=48$)
Cavities of >4 cm in aggregate*	*n* (%)	8 (57.1)	6 (46.2)	10 (66.7)	1 (16.7)	25 (52.1)
Disease extent of more than one hemithorax†	*n* (%)	5 (35.7)	4 (30.8)	6 (40.0)	3 (50.0)	18 (37.5)

Definition of abbreviations: BMI = body mass index; SOC = standard of care.
The table shows the baseline characteristics of participants in the four study groups.
*A cavity is defined as a lucency completely surrounded by parenchymal opacification of ⩾1 cm diameter in its maximum dimension.
†Extent of disease is defined as involving a total lung area of less than one-quarter of the entire thoracic cavity, more than one-quarter but less than one-half, or more than a hemithorax.

log_{10}(cfu) collected from serial sputum cultures for each patient. No significance testing was done. PK data are presented as descriptive analyses.

Results

Participants

A total of 64 participants were enrolled, of whom 61 initiated treatment on telacebec 100 mg ($n=18$), 200 mg ($n=17$), 300 mg ($n=17$), or SOC ($n=9$); 58 participants completed treatment, of whom 51 were included in the PPROT analysis (Figure 2). Participants were mostly young, HIV-negative men, were borderline underweight, were of Black or mixed race, and had unilateral cavitary TB (Table 1). Treatment arms were well matched.

Activity and Microbiology

SOC showed the expected fall in sputum mycobacterial load, thereby validating the laboratory assays. All cultures were confirmed as pan-susceptible *M. tuberculosis* by genetic and phenotypic susceptibility testing. All telacebec doses showed reductions in bacterial load from baseline with both EBA_{TTP} and EBA_{cfu}. The mean (SD) daily changes in EBA_{TTP} and EBA_{cfu} are shown in Table 2 and Figure 3 for the PPROT population. The 300-mg dose demonstrated greater EBA than the 100-mg dose and was about half the magnitude of SOC (Table 2). Telacebec activity increased

Table 2. Early Bactericidal Activity per Treatment Arm

Daily Rate of Change in Log_{10}(cfu) Count from Day 0 to Day 14	EBA_{cfu}(0–14)	EBA_{cfu}(0–2)	EBA_{cfu}(2–14)
100 mg telacebec ($n=15$)	0.024 (0.067)	0.086 (0.167)	0.014 (0.075)
200 mg telacebec ($n=15$)	0.071 (0.056)	0.107 (0.193)	0.066 (0.059)
300 mg telacebec ($n=15$)	0.101 (0.058)	0.074 (0.209)	0.105 (0.080)
SOC ($n=6$)	0.214 (0.034)	0.346 (0.117)	0.192 (0.043)
Daily Percentage Change in TTP from Day 0 to Day 14	**EBA_{TTP}(0–14)**	**EBA_{TTP}(0–2)**	**EBA_{TTP}(2–14)**
100 mg telacebec ($n=15$)	1.76 (1.28)	3.50 (4.43)	1.48 (1.37)
200 mg telacebec ($n=15$)	2.10 (1.94)	5.32 (6.68)	1.60 (1.91)
300 mg telacebec ($n=15$)	3.87 (2.88)	4.68 (5.37)	3.78 (3.99)
SOC ($n=6$)	6.03 (1.44)	11.65 (5.88)	5.14 (1.30)

Definition of abbreviations: cfu = colony-forming units; EBA = early bactericidal activity; SOC = standard of care; TTP = time to positivity.
The table 2 shows the daily rate of change in log_{10}(cfu) count and the percentage of change in time to positivity from Day 0 to Day 14. Data are expressed as mean (SD). The highest activity was observed in the group receiving the highest dose of telacebec (300 mg).

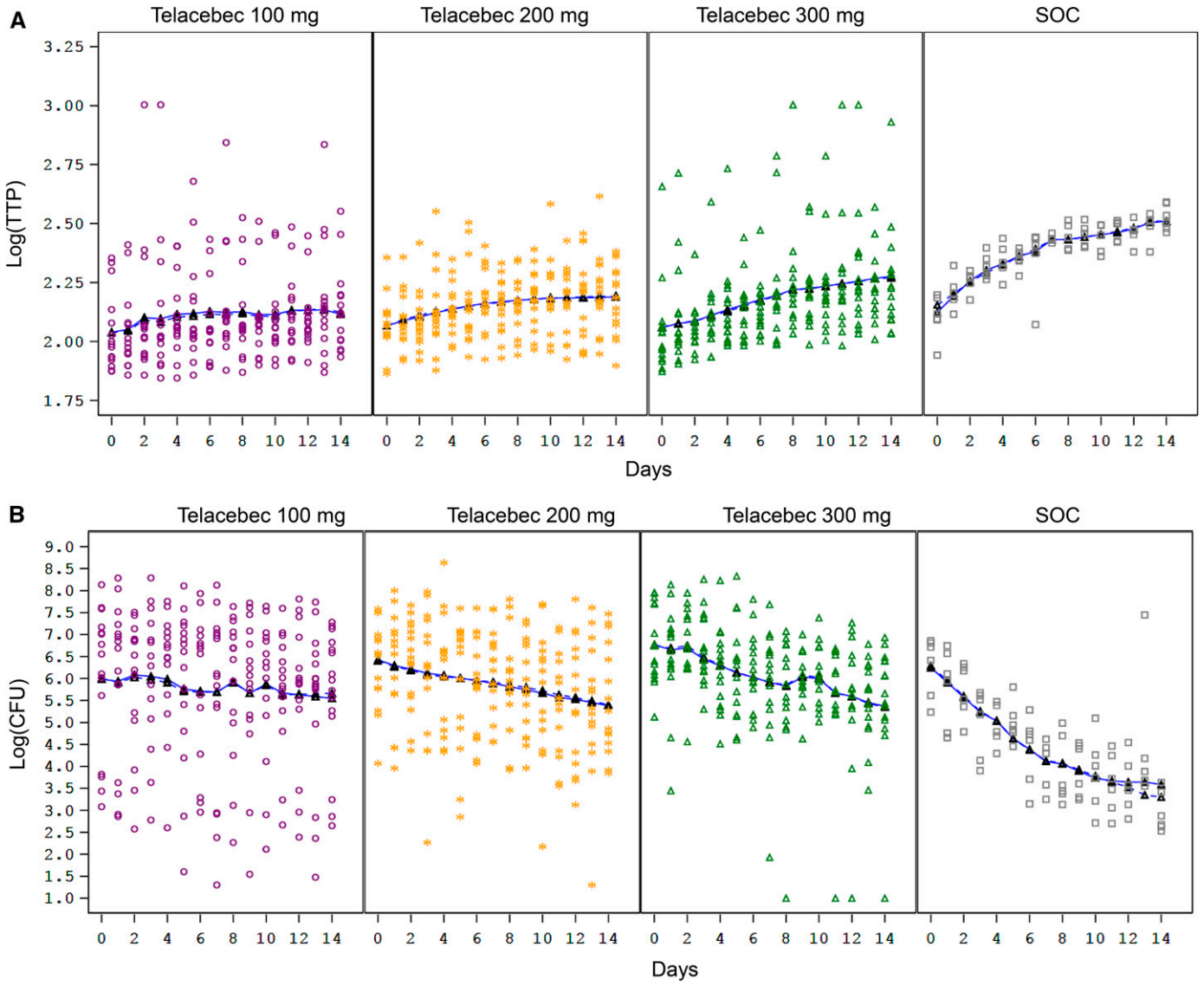

Figure 3. Bactericidal activity of telacebec and SOC. (*A*) Observed and fitted log(time to positivity [TTP]) over time for all respective study groups in the per protocol population. (*B*) Observed and fitted log(colony-forming units [cfu]) over time for all respective study groups in the per protocol population. Lines were fitted using nonlinear regression modeling with log(TTP) and log(cfu) collected from serial sputum cultures for each patient. Overall, telacebec showed a dose-dependent increase in antitubercular activity. The results for SOC validate the laboratory methods. Purple circles, telacebec 100 mg; yellow stars, telacebec 200 mg; green triangles, telacebec 300 mg; white boxes, Rifafour. SOC = standard of care.

dose proportionally without indication of a plateau. Results were similar for the mITT population. Indications of drug carryover were not seen.

Safety and Tolerability

A total of 36 (63.5%) participants in the telacebec arms (mITT) experienced one or more AEs compared with 9 (100%) in the control arm; most AEs were considered mild (38 participants [62.3%]). One participant was withdrawn for a severe AE of worsening TB, which occurred in the telacebec 100 mg group and was considered unlikely related to study drug. The only other serious AE was observed in a participant with hemoptysis before any doses of study drug. AEs across study groups are shown in Table 3. Laboratory results, vital signs, and ECG measurements showed nonsignificant variation over time and among study groups. No AEs reported for these assessments were related to the study drug. Importantly, no dose-dependent increase in AEs was observed across the telacebec arms.

PK Profile and Pharmacodynamics

In the telacebec 100–300 mg dose range, plasma telacebec maximum concentration and total exposure (area under the concentration–time curve from time 0 to the 24-hour time point) increased proportionally with dose, both after a single dose on Day 1 and after multiple doses on Day 14 (Table 4). With daily telacebec dosing, accumulations in plasma exposures were approximately twofold for maximum concentration and threefold for area under the concentration–time curve from time 0 to the 24-hour time

Table 3. Adverse Events

	Telacebec			SOC	Total
	100 mg (*n* = 18)	200 mg (*n* = 17)	300 mg (*n* = 17)	(*n* = 9)	(*n* = 61)
Patients with at least 1 AE	12 (66.7)	12 (70.6)	9 (52.9)	9 (100.0)	42 (68.9)
Skin and subcutaneous tissue disorders	6 (33.3)	5 (29.4)	3 (17.6)	2 (22.2)	16 (26.2)
Pruritus	3 (16.7)	0	1 (5.9)	1 (11.1)	5 (8.2)
Rash pruritic	1 (5.6)	2 (11.8)	1 (5.9)	0	4 (6.6)
Pruritus generalized	1 (5.6)	1 (5.9)	1 (5.9)	0	3 (4.9)
Gastrointestinal disorders	4 (22.2)	3 (17.6)	6 (35.3)	2 (22.2)	15 (24.6)
Abdominal pain	1 (5.6)	1 (5.9)	2 (11.8)	0	4 (6.6)
Diarrhea	2 (11.1)	1 (5.9)	1 (5.9)	0	4 (6.6)
Dyspepsia	1 (5.6)	1 (5.9)	1 (5.9)	0	3 (4.9)
Nausea	0	1 (5.9)	1 (5.9)	1 (11.1)	3 (4.9)
Vomiting	1 (5.6)	0	1 (5.9)	1 (11.1)	3 (4.9)
Nervous system disorders	3 (16.7)	4 (23.5)	2 (11.8)	3 (33.3)	12 (19.7)
Dizziness	1 (5.6)	4 (23.5)	1 (5.9)	1 (11.1)	7 (11.5)
Headache	2 (11.1)	2 (11.8)	1 (5.9)	1 (11.1)	6 (9.8)
Musculoskeletal and connective tissue disorders	2 (11.1)	5 (29.4)	2 (11.8)	2 (22.2)	11 (18.0)
Back pain	2 (11.1)	1 (5.9)	1 (5.9)	0	4 (6.6)
Arthralgia	0	1 (5.9)	0	2 (22.2)	3 (4.9)
Musculoskeletal pain	0	2 (11.8)	1 (5.9)	0	3 (4.9)
Respiratory, thoracic and mediastinal disorders	2 (11.1)	1 (5.9)	4 (23.5)	2 (22.2)	9 (14.8)
Hemoptysis	2 (11.1)	1 (5.9)	4 (23.5)	1 (11.1)	8 (13.1)
Deteriorating TB	1 (5.6)	0	0	0	1 (1.6)
Epistaxis	0	0	2 (11.8)	1 (11.1)	3 (4.9)

Definition of abbreviations: AE = adverse event; SOC = standard of care; TB = tuberculosis.
The table shows AEs, defined as AEs that started or worsened on or after the first study drug administration up to the last scheduled visit, for the modified intent to treat population. AEs were coded using the Medical Dictionary for Regulatory Activities version 19.1. Data are expressed as *n* (%). Most AEs were mild. One participant reported a severe AE of worsening TB leading to study withdrawal.

point by Day 14 (Table 4). The half-life of telacebec was 9–13 hours over the doses evaluated. Trough concentrations were rising up to 14 days and were dose proportional, which means that in this study, steady-state conditions were not reached (Figure 4). Only a negligible fraction of the telacebec dose was recovered in urine as the parent drug telacebec (mean excreted fraction over 24 h 0.0002–0.0004%), suggesting renal clearance as a minor route of elimination. All patients had plasma telacebec concentrations above the actuarial MIC_{50} of 2.7 nM for the entire 24-hour dosing interval. PK/EBA correlation coefficients were variable between treatment arms and generally small and not significant.

Telacebec in Combination with Other Drugs in a Murine Model

In Balb/c mice infected with *M. tuberculosis* H37Rv, there was a significant decrease in cfu in lungs and spleen of mice treated for four weeks with telacebec, BDQ, and linezolid, but not for SQ109 (Figure 5). There was increased antitubercular activity when telacebec and BDQ were combined, whereas the other combinations did not show signs of synergism; the telacebec/linezolid and telacebec/SQ109 combinations showed an indication of antagonism.

Discussion

Telacebec demonstrated antimycobacterial activity over 14 days of treatment in participants with smear-positive pulmonary TB. Activity was seen at the lowest dose of 100 mg and increased proportionally to the highest dose of 300 mg. There were only mild to moderate AEs, which were evenly distributed across the doses. Telacebec's PK profile allows once-daily dosing and supports exploration of intermittent dosing in further studies.

The use of both liquid and solid culture methods for quantifying the sputum mycobacterial load was helpful to resolve two potential methodological limitations. First, the validity of TTP as a primary endpoint for drugs interfering with the *M. tuberculosis* respiratory chain, such as telacebec, can be challenged (14). As the Mycobacteria Growth Indicator Tube system is based on detection of mycobacterial metabolism depending on V_{O_2}, drugs acting on the *M. tuberculosis* respiratory chain can potentially interfere through either compensatory increases of mycobacterial V_{O_2} or mycobacterial adaptation inhibiting the oxidative phosphorylation pathway, leading to slow respiration (14, 15). Second, agents with very low MIC and good tissue penetration can lead to drug carryover into sputum, potentially influencing cfu counts at the high doses late in the treatment period (16). Such an effect was not seen upon inspection of the dilution series, where counts at lower dilutions would cause a sudden drop instead of an increase proportional to the dilution factor. Increasing TTP correlated well with decreasing cfu counts in all telacebec doses as well as SOC, thereby confirming the validity of both readouts.

The time to steady state was longer than expected from $t_{1/2}$ values calculated on Day 1 of this study and previous results in phase I studies (10, 11). A time-dependent decrease in telacebec clearance from plasma was observed. However, this is likely an artifact due to underestimation of $t_{1/2}$ and area under the concentration–time curve from the time of dosing extrapolated to infinity on Day 1 in our study compared with the phase I single-dose escalation study. In the phase U single-dose escalation study, a 30-fold longer $t_{1/2}$ and a 3-fold higher area under the concentration–time curve from the time of dosing extrapolated to infinity were reported

Table 4. Pharmacokinetic Characteristics of Telacebec

Parameter	Telacebec 100 mg		Telacebec 200 mg		Telacebec 300 mg	
	n	Geometric Mean (CV%)	*n*	Geometric Mean (CV%)	*n*	Geometric Mean (CV%)
Single dose, Day 1						
C_{max}, ng/ml	15	281.77 (42.4)	15	691.13 (64.9)	15	867.37 (41.6)
t_{max}, h*	15	4.000 (3.00–6.02)	15	4.000 (3.00–6.08)	15	4.020 (3.00–8.00)
$AUC_{0–24}$, ng · h/ml	15	2163 (46.9)	15	5104 (76.9)	15	7232 (38.9)
$AUC_{0–inf}$, ng · h/ml	10	2469 (47.0)	13	5743 (83.7)	11	9384 (38.5)
$t_{1/2}$, h	13	10.66 (51.9)	13	8.897 (20.5)	12	12.82 (177.2)
CL/F, L/h	10	40.50 (47.0)	13	34.85 (83.7)	11	31.96 (38.6)
V_z/F, L	10	505.1 (61.9)	13	447.1 (80.9)	11	421.7 (44.3)
C_{max}/D, ng/ml/mg	15	2.8177 (42.4)	15	3.4559 (64.9)	15	2.8914 (41.6)
$AUC_{0–24}$/D, ng · h/ml/mg	15	21.63 (46.9)	15	25.52 (76.9)	15	24.10 (38.8)
Multiple dose, Day 14						
C_{max}, ng/ml	15	616.64 (45.6)	15	1471.9 (41.3)	15	1794.6 (60.6)
t_{max}, h*	15	4.000 (2.98–6.13)	15	4.000 (3.00–6.00)	15	4.000 (3.00–6.02)
C_{min}, ng/ml	15	144.83 (51.5)	15	363.80 (76.4)	15	604.38 (61.4)
C_{avg}, ng/ml	15	272.0 (47.8)	15	679.9 (61.0)	15	981.6 (63.1)
Fluct, %	15	171.8 (19.4)	15	156.3 (44.3)	15	118.2 (31.2)
$AUC_{0–24}$, ng · h/ml	15	6520 (47.7)	15	16290 (61.0)	15	23580 (63.0)
CL/F, L/h	15	15.34 (47.7)	15	12.27 (61.0)	15	12.74 (63.0)
RC_{max}	15	2.189 (41.1)	15	2.130 (45.3)	15	2.070 (43.2)
$RAUC_{0–24}$	15	3.016 (35.8)	15	3.195 (39.4)	15	3.262 (44.7)
LI	10	2.316 (31.3)	13	2.699 (40.8)	11	2.694 (35.4)
C_{max}/D, ng/ml/mg	15	6.1664 (45.6)	15	7.3602 (41.3)	15	5.9823 (60.6)
$AUC_{0–24}$/D, ng · h/ml/mg	15	65.20 (47.7)	15	81.56 (61.1)	15	78.57 (63.1)

Definition of abbreviations: $AUC_{0–24}$ = area under the concentration–time curve from time 0 to the 24-hour time point; $AUC_{0–inf}$ = area under the concentration–time curve from the time of dosing extrapolated to infinity; CL/F = apparent total body clearance; C_{max} = maximum observed plasma drug concentration; C_{min} = minimum observed plasma drug concentration; CV% = coefficient of variation; D = dose-normalized; Fluct = percent fluctuation; LI = linearity factor; $RAUC_{0–24}$ = accumulation ratio for AUC(0-24); RC_{max} = accumulation ratio for C_{max}; $t_{1/2}$ = apparent terminal elimination half-life; t_{max} = time of maximum observed concentration; V_z/F = apparent volume of distribution after oral administration. The table shows a summary of key plasma telacebec pharmacokinetic parameters for the per protocol population on Day 1 and Day 14.
*Median (range).

(10). This difference is explained by a longer PK sampling interval in the single-dose phase I study (312 vs. 24 h in our study); the effective $t_{1/2}$ in the multiple dose phase I study (with PK sampling intervals similar to those in our study) was only threefold higher. Significant accumulation did occur, supporting intermittent or shorter dosing regimens. An ongoing phase II trial for Buruli ulcer is investigating 300 mg/d dosing for 28 days (NCT 06481163). Information about drug exposure beyond 2 weeks will help determine the right dose for longer applications treatment durations such as needed for TB.

This clinical trial was uneventful, and there were no limitations other than the well-known uncertainty how promising results from 2-week studies will translate into longer duration regimens. Building blocks for such regimens could be constructed with other agents targeting the energy production of *M. tuberculosis*. Telacebec acts through inhibition of the respiratory cytochrome bc1 complex (Figure 1). BDQ inhibits ATP synthase by binding to subunit c (17), and clofazimine (CFZ) acts as a prodrug, which is reduced by reduced nicotinamide adenine dinucleotide dehydrogenase, to release reactive oxygen species upon reoxidation by O_2 (18). Exposure of mycobacteria to BDQ and telacebec causes increased Vo_2 to compensate for the decreased ATP synthase function. This increases the production of reactive oxygen species triggered by CFZ (15). In mice with acute TB, there was a synergistic reduction in cfu counts in both lungs and spleen when treated with the telacebec/BDQ combination, but not when telacebec was combined with other agents (Figures 5A and 5B). From a biomechanical perspective, this synergistic activity should also exist for newer diarylquinolines, but this remains to be confirmed. *In vitro*, the synergistic combination of BDQ/telacebec potentiates the mycobacterial killing activity of CFZ, both in time-kill assays and human cell lines (15). Whether CFZ synergizes with this drug combination in *in vivo* models of TB remains to be confirmed.

The concept of inhibition of mycobacterial energy production can be expanded to other mycobacteria, including nontuberculous mycobacteria (NTM), which are an expanding global problem (19). NTM are a heterogeneous group of pathogenic and nonpathogenic environmental mycobacteria (20). Although the most common NTM causing human disease (*M. avium*, *M. intracellulare*, and *M. abscessus*) show high MICs to telacebec (21, 22), the drug has potential for treatment of mycobacterial infections Buruli ulcer (caused by *M. ulcerans*) and leprosy (*M. leprae*) that are both classified by the World Health Organization as neglected tropical diseases and continue to cause substantial morbidity in endemic countries (23, 24).

Buruli ulcer substantially affects children and adolescents, with 40% of cases occurring in patients <15 years of age in Africa (23). Current guidelines recommend 8 weeks of treatment combining rifampicin and clarithromycin. Telacebec showed an MIC_{50} of less than 1 nM in the classical African and Australian strains of *M. ulcerans* (25) that cause the vast majority of global

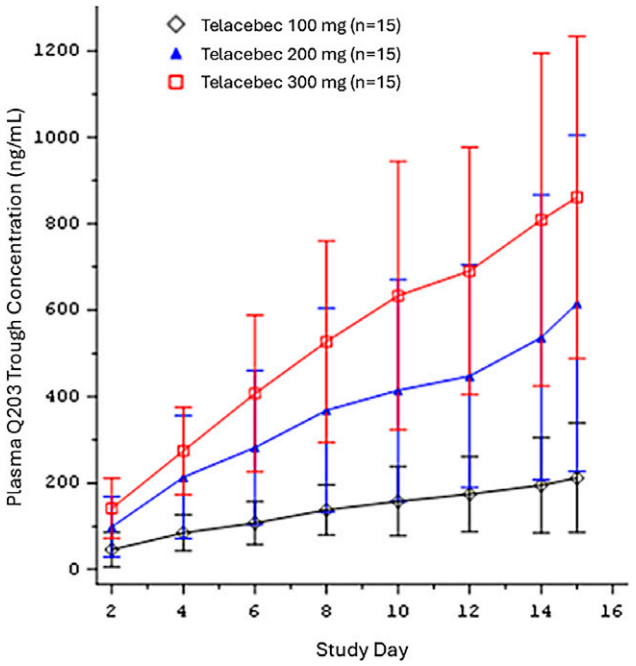

Figure 4. Plasma trough concentrations of telacebec over time. The figure shows mean (SD) plasma trough concentrations of telacebec over the course of the study. Gray line and diamonds, telacebec 100 mg; blue line and triangles, telacebec 200 mg; red line and squares, telacebec 300 mg. Q203 = telacebec.

cases and four- to eightfold higher against Japanese ancestral lineage isolates (25). Several studies have shown telacebec's activity in a mouse footpad model with classical strains of *M. ulcerans* (25–30), outperforming that of rifampin alone (25) or in combination with streptomycin in reduction of clinical signs and bacterial load (26). In mice, telacebec for 2 weeks had good clinical outcomes (29), and single doses of 20 mg/kg (equivalent to 300 mg in humans) and four weekly doses of 5 mg/kg rapidly diminished bacterial load and symptoms of inflammation in the mouse footpad model, with no relapse at 19 weeks after treatment (27). A single-dose treatment for Buruli ulcer with telacebec seems to be within reach and could significantly reduce disease burden and associated costs.

Leprosy still occurs in more than 120 countries, with 200,000 new cases reported every year (24). Leprosy affects the skin, the peripheral nerves, mucosa of the upper respiratory tract, and the eyes; the disease causes physical deformities, leading to stigmatization and discrimination. A multidrug regimen including rifampicin, dapsone, and CFZ is prescribed for 6–12 months, with few alternative options for treatment intolerance or resistance. Telacebec showed high nanomolar potency against extracellular *M. leprae in vitro* as well as in a macrophage infection model (31). In a mouse footpad model of infection, telacebec was compared with rifampin monotherapy. Although more than five consecutive doses of rifampin were needed to detect a bactericidal efficacy, one low dose of telacebec (2 mg/kg) was sufficient to substantially reduce bacterial viability (31).

Telacebec's potency against *M. ulcerans* and *M. leprae* is explained by the fact that these mycobacteria have lost genes encoding a functional cytochrome bd oxidase (25, 32). Lacking alternative terminal oxidases, they rely exclusively on the cytochrome bcc:aa3 terminal oxidase, the target of telacebec and related drugs (Figure 1) (25). The aforementioned findings from animal studies

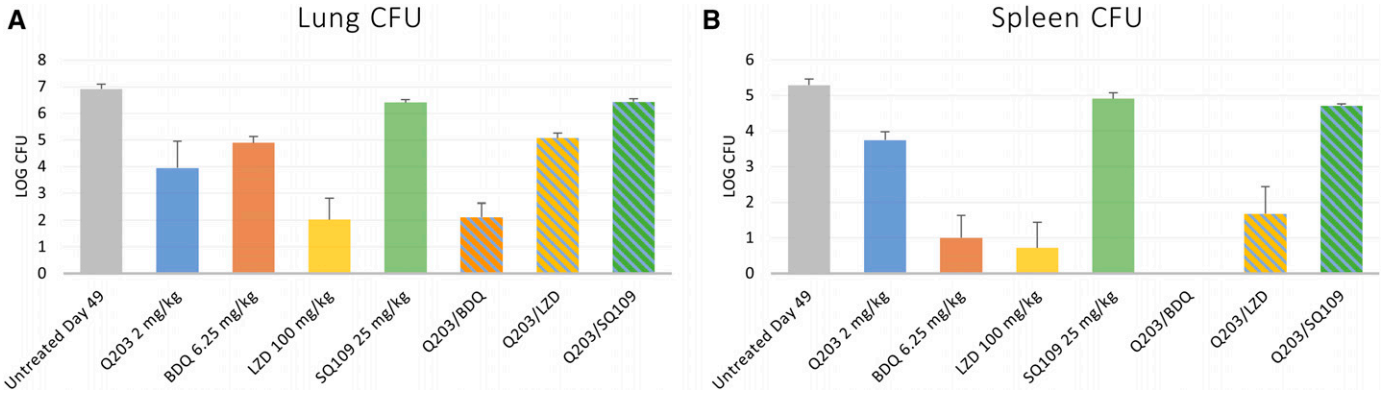

Figure 5. Murine studies indicate synergistic anti–*Mycobacterium tuberculosis* activity of telacebec (Q203) combined with bedaquiline (BDQ). Q203 was tested in combination with BDQ, linezolid, and SQ109 in a mouse model of acute tuberculosis infection (Institut Pasteur Korea, Gyeonggi-do, Korea). Balb/c mice were infected with *M. tuberculosis* H37Rv intranasally to obtain an inhaled dose of 100–200 colony-forming units (cfu) 3 weeks before the initiation of study treatment. Study drugs were administered once daily (5 d/wk) for 4 weeks; there were eight study groups ($n = 5$ each): *1*) untreated (gray bars); *2*) Q203 2 mg/kg (blue bars); *3*) BDQ 6.25 mg/kg (orange bars); *4*) linezolid (LZD) 100 mg/kg (yellow bars); *5*) SQ109 25 mg/kg (green bars); *6*) Q203/BDQ combination (blue/orange-striped bars); *7*) Q203/LZD combination (blue/yellow-striped bars); and *8*) Q203/SQ109 combination (blue/green-striped bars). The doses in the combination groups were the same as in the monotherapy groups. After 4 weeks, mice were killed, and lung and spleen homogenates were assessed for cfu counts. (*A* and *B*) The figure shows cfu in lung (*A*) and spleen (*B*) homogenates. There was increased antitubercular activity when Q203 and BDQ were combined, whereas the other combinations did not show signs of synergism; the Q203/LZD and Q203/SQ109 combinations showed an indication of antagonism.

are supportive of further clinical testing of telacebec to shorten and improve treatment regimens for Buruli ulcer and leprosy.

Conclusions

In summary, telacebec remains a promising candidate for the treatment of patients with mycobacterial infections. The study presented here delivered clinical proof of concept for TB. An exclusive license agreement was recently signed between the developing pharmaceutical company, Qurient, and the TB Alliance, to advance telacebec toward clinical trials that would combine it with other anti-TB drugs to form novel candidate regimens. Nonclinical studies showed great potential for telacebec in the treatment of Buruli ulcer and leprosy with the potential to dramatically shorten treatment. The ongoing development of new chemical entities such as telacebec in an era of antimicrobial resistance underscores the importance of continued investment in antimicrobial research. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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