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Dear Dr. Woodcock and Dr. Farley:

The following comments from Public Citizen's Health Research Group are being sent in response to New Drug Application (NDA) #204-834 — submitted by Janssen Research and Development ("Janssen") and considered by the Food and Drug Administration's (FDA's) Anti-Infective Drugs Advisory Committee (AIDAC) meeting on November 28, 2012 — for bedaquiline as part of a combination-drug regimen for treatment of multi-drug resistant tuberculosis (MDR-TB).

We strongly oppose accelerated approval of the NDA for bedaquiline based on a single phase 2, randomized, placebo-controlled clinical trial of bedaquiline in subjects with MDR-TB showing improvement in the surrogate endpoint of sputum culture conversion when the data from that same clinical trial revealed a mortality rate — clearly the most important clinically relevant outcome for a life-threatening disease — that was *five times higher* in subjects assigned to the bedaquiline group in comparison to those assigned to the placebo group.

It is not possible to conclude that a surrogate endpoint is "reasonably likely" to predict benefit for patients — as required by FDA regulations — when the same clinical trial of a drug using that surrogate endpoint shows a significant increase in mortality, regardless of the drug's effects on the surrogate marker. The only reasonable conclusion in such cases is that the selected surrogate endpoint is, in fact, not a valid or useful marker of clinical benefit; its surrogate "benefit" is trumped by increases in the adverse clinical outcome — death — nullifying the use of the favorable surrogate marker as a means of granting accelerated approval.

Approval of bedaquiline under an accelerated approval process based on the currently available evidence would endanger public health, and the NDA for this drug should never have been brought to the AIDAC for consideration. In the face of clinical evidence of increased deaths, including deaths from tuberculosis (TB) or TB-related causes in patients getting bedaquiline, compared to those getting a placebo, it is not possible to give accelerated approval to the drug. We urge you to reject the dangerous possibility of such an accelerated approval.

I.   Background

a. MDR-TB

MDR-TB is defined as TB organisms resistant to both isoniazid and rifampin, two first-line drugs for TB. MDR-TB strains that are also resistant to an injectable aminoglycoside and a fluoroquinolone are classified as extremely drug resistant TB (XDR-TB).[1]

MDR-TB is a serious and life-threatening disease: The FDA noted that mortality rates were as high as 100% in early reports.[2] Janssen reported the following more recent mortality data for MDR-TB:[3]

> For patients starting treatment for MDR-TB in 2007, countries reported deaths in 4%‑45% (median: 11%). Two independently conducted meta[-]analyses from 2009, each including approximately 30 studies in MDR-TB, found death as a reported outcome in 11% of treated patients. An even more recent meta-analysis reflecting data from [9,143] individual patients reported a mortality rate of 15%.

Janssen also referenced 150,000 deaths worldwide in 2008.[4]

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[1] The Food and Drug Administration. Briefing Package: NDA 204-384 FDA Anti-Infective Drugs Advisory Committee Meeting. November 28, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329258.pdf. Accessed December 19, 2012.

[2] *Ibid*.

[3] Janssen. Briefing Document: TMC207 (bedaquiline); Treatment of Patients with MDR-TB, NDA 204-284. 28 November 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf. Accessed December 19, 2012.

The FDA noted the following regarding the treatment of drug resistant TB:[5]

> Nonetheless, treatment for resistant TB is complex, costly, toxic and prolonged, requiring at least 5 second-line drugs for up to 2 years. Second-line drugs include injectable drugs (amikacin, kanamycin, capreomycin) and oral fluoroquinolones (FQs) and other second line drugs; the optimal use of which has not been well studied in randomized controlled trials and **whose safety when used in concert with various doses and regimens is not sufficiently described**. [emphasis added]

b. Bedaquiline

Bedaquiline is a new chemical entity and first-in-class compound that inhibits the proton pump of mycobacterial adenosine 5'-triphosphate (ATP)-synthase 3.[6] Bedaquiline thereby inhibits the production of energy in mycobacterial cells, resulting in cell death.

The proposed recommended dose of the drug for treatment of pulmonary MDR-TB is administered orally at a dose of 400 milligrams (mg) once a day for two weeks, followed by 22 weeks of intermittent dosing at 200 mg three times a week, for a total duration of 24 weeks.[7] The drug is administered orally with food and in combination with other anti-TB medications that would be administered for 18 to 24 months.[8]

The drug accumulates in tissues and has a prolonged half-life, reaching peak exposures in 8 weeks and a terminal half-life of 4 to 5 months. The drug also has a major metabolite, *N*-monodesmethyl-bedaquiline, and the terminal half-life for this metabolite is approximately 5.5 months.[9]

Bedaquiline was developed in an attempt to improve outcomes in MDR-TB patients given the sub-optimal effectiveness and toxicity of currently available regimens for treating this disease.

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[4] *Ibid*.

[5] The Food and Drug Administration. Briefing Package: NDA 204-384; FDA Anti-Infective Drugs Advisory Committee Meeting. November 28, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329258.pdf. Accessed December 19, 2012.

[6] *Ibid*.

[7] Janssen. Briefing Document: TMC207 (bedaquiline); Treatment of Patients with MDR-TB, NDA 204-284. 28 November 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf. Accessed December 19, 2012.

[8] *Ibid*

[9] The Food and Drug Administration. Briefing Package: NDA 204-384; FDA Anti-Infective Drugs Advisory Committee Meeting. November 28, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329258.pdf. Accessed December 19, 2012.

c. Regulatory background

The FDA indicated that bedaquiline is being considered for accelerated approval under FDA regulations at 21 C.F.R. part 314, subpart H. These regulations state that:

> This subpart applies to certain new drug products that have been studied for their safety and effectiveness in treating **serious or life-threatening illness** and that provide **meaningful therapeutic benefits to patients over existing treatments**.[10]

The FDA regulations at 21 C.F.R. part 314, subpart H goes on to state that:

> FDA may grant marketing approval for a new drug product on the basis of adequate and well-controlled clinical trials establishing that the drug product has an effect on a surrogate endpoint that is **reasonably likely, based on epidemiologic, therapeutic, pathophysiologic, or other evidence, to predict clinical benefit** or on the basis of an effect on a clinical endpoint other than survival or irreversible morbidity. Approval under this section will be subject to the requirement that the applicant study the drug further, to verify and describe its clinical benefit, where there is uncertainty as to the relation of the surrogate endpoint to clinical benefit, or of the observed clinical benefit to ultimate outcome.[11]

II. Randomized, Controlled Clinical Trial Demonstrated that Bedaquiline Used at the Recommended Dose and Duration Increased Mortality and That the Chosen Surrogate Endpoint Is Not "Reasonably Likely to Predict Clinical Benefit" in Patients with MDR-TB

a. Design of the phase 2 randomized clinical trials

Bedaquiline was studied in two consecutive phase 2, randomized, placebo-controlled, add-on superiority trials identified collectively as study C208. For both trials, the experimental group subjects received bedaquiline plus a standard multi-drug anti-TB regimen, whereas the control group subjects received placebo plus a standard multi-drug anti-TB regimen.[12] Therefore, subjects in the control groups received a standard combination of currently available drugs for treating MDR-TB.

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[10] 21 C.F.R. § 314.500. Emphasis added.

[11] 21 C.F.R. § 314.510. Emphasis added.

[12] The Food and Drug Administration. Briefing Package: NDA 204-384; FDA Anti-Infective Drugs Advisory Committee Meeting. November 28, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329258.pdf. Accessed December 19, 2012.

Stage 1 of study C208 was an exploratory-stage trial, in which subjects received bedaquiline or placebo for 8 weeks as add-on to a standard background regimen of anti-TB drugs given for 18 to 24 months. Final follow-up for Stage 1 was 104 (8+96) weeks after initiation of the drug regimen.[13] Stage 1 was completed by the time of the AIDAC meeting on November 28. Of note, this stage does not provide evidence on the safety and efficacy of the drug under the recommended use of the drug in clinical practice (i.e., 24-week duration) as proposed by Janssen.

Stage 2 of study C208 was a proof-of-efficacy trial. Stage 2 subjects received bedaquiline or placebo for 24 weeks added onto a standard background regimen of anti-TB drugs given for 18 to 24 months. Follow-up continued out to 96 weeks after the end of the bedaquiline/placebo treatment period (24+96=120 weeks) and approximately 6 months after the end of all TB treatment.[14] Stage 2 is ongoing, but complete follow-up data out to 72 weeks on all subjects — unless they discontinued study prior to 72 weeks — were available at the time of the AIDAC meeting. This single ongoing phase 2 study is the sole evidence related to how the drug would be used in patients in clinical practice.

The primary endpoint for both Stage 1 and Stage 2 of study C208 was the surrogate endpoint of time to sputum culture conversion at the end of the bedaquiline/placebo treatment period. Time to sputum culture conversion was based on the qualitative assessment of culture growth in mycobacteria growth indicator tube using spot sputum samples. Sputum culture conversion was defined as two consecutive negative cultures from sputa.[15]

b. Results of the phase 2 randomized clinical trials

Only 47 subjects in South Africa were enrolled in Stage 1 of study C208 (23 received bedaquiline, 24 received placebo). The time to sputum culture conversion by 8 weeks was faster in the bedaquiline group. The difference in the rate of culture conversion between the groups was statistically significant at week 8 but not at later time points. Two subjects died in each group.[16]

In Stage 2 of study C208, 161 subjects were randomized to either the bedaquiline group (n=80) or the placebo group (n=81). One subject, randomized to the bedaquiline group but not treated, was excluded from the analysis. Subjects were enrolled in sites in Eastern Europe, Asia, South America, and South Africa. The data for this trial showed faster time to sputum culture conversions at 24 weeks in the bedaquiline-group subjects compared to the placebo-group subjects (see table 11 below, excerpted from the FDA briefing package). Similar to Stage 1, the

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[13] *Ibid.*

[14] *Ibid.*

[15] *Ibid.*

[16] *Ibid.*

difference in culture conversion rates at the later time point at 72 weeks was no longer statistically significant.[17]

Table 11. C208 - Stage 2 Culture Conversion Rates at Week 24 – mITT

Microbiologic Status	Bedaquiline N=66	Placebo N=66	p-value 95% CI
Week 24 Treatment success	52/66 (79%)	38/66 (58%)	0.009 [5.7%, 36.7%]
Week 72 Treatment success	47/66 (71%)	37/66 (56%)	0.070 [-1.1%, 31.4%]

Source: Modified from NDA 204,384. Original Submission. Complete Study Report – Stage 2 – Interim analysis. p. 144, 164

In contrast to the apparent benefit seen with the surrogate endpoint of time to sputum culture conversion, the safety data from Stage 2 of study C208 showed a statistically significant increase in the mortality rate with bedaquiline when added to a standard anti-TB regimen and used for the recommended duration proposed by Janssen, in comparison to standard anti-TB therapy alone. The data on subject deaths in study C208 was clearly presented by Janssen (see table 44 below, excerpted from the sponsor's briefing document for the November 28 AIDAC meeting; "TMC207" is the designation for bedaquiline).[18]

Table 44:   Pooled C208 Stage 1 and Stage 2 Trials: Overview of Deaths

	TMC207	Placebo
C208 Stage 1	N = 23	N = 24
During Trial	1	0
Follow-up of Premature Withdrawals	1	2
Total	2	2
C208 Stage 2[a]	N = 79	N = 81
During Trial	6	1
Follow-up of Premature Withdrawals	4	1
Total	10	2
Pooled C208 Stage 1 and 2	N = 102	N = 105
	12	4

Data on file, Janssen Research and Development

For the Stage 2 trial — which used bedaquiline for 24 weeks, the recommended duration proposed by Janssen — these results show a death rate of 10/79 subjects (12.7%) in the bedaquiline group compared to 2/81 subjects (2.5%) in the control group. This represents an absolute increase of 10.2% (95% confidence interval [CI], 2.1% to 19.7% - p=.017) in the death

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[17] *Ibid*.

[18] Janssen. Briefing Document: TMC207 (bedaquiline); Treatment of Patients with MDR-TB, NDA 204-284. 28 November 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf. Accessed December 19, 2012.

rate when bedaquiline is added to standard therapy, as well as a five-fold relative increase. This translates into a number needed to harm (NNTH) (i.e., kill) of 10 (95% CI, 5 to 50).[19] A NNTH of 10 would mean that for every 10 patients administered bedaquiline in addition to standard anti-TB therapy, rather than standard anti-TB therapy alone, one patient will die.

c. Result of Stage 2 of study C208

MDR-TB obviously is a serious and life-threatening disease for which new drugs are needed. However, the data from study C208 failed to demonstrate that bedaquiline provides a meaningful therapeutic benefit to MDR-TB patients over existing treatments. On the contrary, the evidence from the only randomized clinical trial testing the drug at the recommended dose and duration demonstrated that there is evidence of clinically significant harm: increased mortality.

The sponsor attempted to discount the mortality data from Stage 2 of study C208 by trying to exclude bedaquiline as a cause of the subjects' death, suggesting that the imbalance in deaths was due to chance. The study investigators concluded that the deaths of the bedaquiline-group subjects were unrelated to study participation in nine cases and doubtfully related in the other.[20] However, three of these bedaquiline-treated subjects had relapsed and died from TB, and two bedaquiline-treated subjects never had sputum conversion and died from TB.[21] It is certainly plausible that these deaths were due to failure of the TB drug regimen that included bedaquiline, even if the mechanism for this poorer outcome is not understood.

Furthermore, for the five deaths attributed to alcohol poisoning (one case), hepatitis/hepatitis cirrhosis (one case), septic shock/peritonitis (one case), cerebrovascular accident (one case), and motor vehicle accident (one case),[22] bedaquiline cannot be ruled out as a potential contributing cause based on the available data, especially given the paucity of human clinical data with this new experimental drug. Indeed, the data presented at the AIDAC meeting showed a number of toxicities associated with bedaquiline in both pre-clinical and clinical testing including cardiac, muscle, and liver toxicity.[23] Given that bedaquiline belongs to an entirely new class of drugs, it is entirely feasible that death in some cases was due to some unmeasured toxicity of the drug. The FDA review seemed to focus primarily on ascertaining the cause of death in patients who died and stating the "association could not be explained" if no direct cause of death related to TB or a

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[19] CI calculated using method described in: Altman D. Confidence intervals for the number needed to treat. Br Med J. 1998;317(7168):1309-12.

[20] Janssen. Briefing Document: TMC207 (bedaquiline); Treatment of Patients with MDR-TB, NDA 204-284. 28 November 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329260.pdf. Accessed December 19, 2012.

[21] *Ibid.*

[22] *Ibid.*

[23] The Food and Drug Administration. Briefing Package: NDA 204-384; FDA Anti-Infective Drugs Advisory Committee Meeting. November 28, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329258.pdf. Accessed December 19, 2012.

measured drug toxicity could be found. However, a known drawback of the use of surrogate endpoints is their lack of ability to predict unmeasured toxicities.[24]

During the AIDAC meeting, the FDA medical reviewer offered the following key conclusions during her presentation of the safety data from the bedaquiline clinical trials:[25]

- A greater number of deaths in the bedaquiline arm is concerning. An etiology of the imbalance could not be determined from the current safety data.

- A major proportion of deaths is attributed to worsening of the underlying condition.

- The role of bedaquiline in deaths where hepatotoxicity and cardiac failure are contributory could not be ruled out. Association is difficult to determine because of the underlying condition, other co-existent medical conditions, and concomitant medications.

Use of the surrogate endpoint of time to sputum culture conversion in clinical trials for treatment of MDR-TB is only useful and appropriate if there is evidence to suggest that this endpoint is "reasonably likely" to serve as a valid predictor of clinically significant benefits, such as reduced mortality or morbidity. The results of Stage 2 of study C208 indicate that time to sputum culture conversion is not a valid predictor of clinically significant benefit.

While the AIDAC agreed in 2009 that sputum culture conversion may be useful as a potential surrogate endpoint for clinical trials evaluating TB treatments,[26] the ultimate utility of a potential surrogate must be evaluated for the particular drug and patient population. The International Conference on Harmonization Guidance E-9, which the FDA helped to develop, states:

> In practice, the strength of the evidence for surrogacy depends upon (i) the biological plausibility of the relationship, (ii) the demonstration in epidemiological studies of the prognostic value of the surrogate for the clinical outcome and (iii) evidence from clinical trials that treatment effects on the surrogate correspond to effects on the clinical outcome. Relationships between clinical and surrogate variables for one product do not necessarily apply to a product with a different mode of action for treating the same disease.[27]

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[24] Fleming TR and DeMets DL. Surrogate endpoints in clinical trials: are we being misled. Ann Intern Med. 1996;125(7):605-13.

[25] The Food and Drug Administration. Slide presentation for the November 28, 2012 meeting of the AIDAC. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM332961.pdf. Accessed December 21, 2012.

[26] The Food and Drug Administration. Summary minutes of the AIDAC. June 3, 2009. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM183845.pdf. Accessed December 20, 2012.

[27] The Food and Drug Administration. Guidance for industry: E9 statistical principles for clinical trials. September 1998.

It is important to reiterate that evidence of harm (i.e., increased mortality) with bedaquiline exposure comes from the only randomized trial testing the drug at the proposed recommended dose and duration of treatment.

Finally, the purpose of randomization is to prevent selection bias and to *causally* relate the outcomes to the drugs administered.[28] The very first randomized clinical trial in TB patients, published 64 years ago, enrolled approximately 50 subjects per group and showed a 20% decrease in mortality in patients receiving streptomycin compared to bed rest.[29] This shows that mortality is a relevant — and the most important — outcome for this serious and life-threatening disease and that an effective drug can have a substantial effect on reducing mortality in a small randomized trial.

III. Conclusions

In conclusion, Public Citizen strongly opposes accelerated approval by the FDA of the NDA for bedaquiline because there is not substantial evidence that the drug is safe and effective. On the contrary, there is substantial evidence that the drug is unsafe. The data from the single, randomized, placebo-controlled phase 2 trial testing bedaquiline at the recommended dose and duration proposed by the sponsor demonstrated a 10% absolute increase and a five-fold relative increase in the mortality rate in subjects treated with bedaquiline plus a standard background regimen of anti-TB drugs compared to control subjects treated with placebo plus a standard background regimen of anti-TB drugs. This included an increase in deaths from TB or TB-related causes in the bedaquiline group. The NNTH when bedaquiline was added to a standard background anti-TB regimen was 10.

Based on these results, there is no scientific, clinical, or ethical justification for approving bedaquiline, and doing so would endanger public health. Before FDA considers approving bedaquiline in the future, the agency must be provided with evidence demonstrating that bedaquiline decreases mortality.

It is astonishing that the FDA even brought this NDA before the AIDAC. The FDA should have issued a complete response letter denying approval based on the available data. It clearly is not possible to conclude that a surrogate endpoint is "reasonably likely" to predict benefit for patients — as required by FDA regulations — when the clinical trial of a drug using that surrogate endpoint shows a significant increase in mortality, regardless of the drug's effects on

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http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM073137.pdf. Accessed December 20, 2012.

[28] Altman DG and Bland JM. Treatment allocation in controlled trials: why randomise? Br Med J. 1999;318:1209.

[29] Medical Research Council. Streptomycin treatment of pulmonary tuberculosis. Br Med J. 1948:2:769.82.

the surrogate marker. The only reasonable conclusion in such cases is that the selected surrogate endpoint is, in fact, not a useful or valid marker of clinical benefit.

Finally, the FDA noted in its briefing document that there is an ongoing phase 3, randomized, placebo-controlled clinical trial of bedaquiline.[30] In view of the mortality data seen in Stage 2 of study C208, the FDA needs to assess whether it is ethical to continue the phase 3 study. Furthermore, if the study is allowed to continue, the FDA should confirm that:

(1) all institutional review boards (IRBs) that are reviewing the phase 3 trial plans have been provided with the mortality data from the phase 2 trial and have assessed if the risks of the research outweigh the potential benefits;
(2) all subjects already enrolled in the phase 3 trial have been informed of the mortality data from the phase 2 trial; and
(3) the IRB-approved informed consent documents for the phase 3 trial clearly describe the mortality data from the phase 2 trial.

Thank you for your prompt attention to this important matter.

Sincerely,

Michael A. Carome, M.D.
Deputy Director
Public Citizen's Health Research Group

Sidney M. Wolfe, M.D.
Director
Public Citizen's Health Research Group

cc: Dr. Margaret Hamburg, FDA Commissioner

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[30] The Food and Drug Administration. Briefing Package: NDA 204-384; FDA Anti-Infective Drugs Advisory Committee Meeting. November 28, 2012. http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Anti-InfectiveDrugsAdvisoryCommittee/UCM329258.pdf. Accessed December 19, 2012.