Minutes of the conference call of
Eurasian Community for Access to Treatment with TB Alliance

October, 3rd 2019, Yerevan, Armenia

Representatives of the organization:

- Stephanie S. Seidel, Senior Manager, Community and Stakeholder Engagement
- Sarah Cook-Scalise, Senior Program Specialist, Market Access

Representative of Mylan:

- Abhishek Datta, Business Development, Mylan Laboratories Limited, Hyderabad, India

Participants:

	Participant	Organisation	Country
1	Igor Chilcevschi	League of PLWH of Moldova	Moldova
2	Andrei Lungu	OA "Initiativa Pozitiva"	Moldova
3	Alex Schneider	Life4me.plus	Switzerland, Russia
4	Nurali Amanzholov	Central Asian Asscoiation of PLWH	Kazakhstan
5	Lyubov Vorontsova	Central Asian Asscoiation of PLWH	Kazakhstan
6	Yelena Rastokina	PF «Answer»	Kazakhstan
7	Sergey Biryukov	PF «AGEP'C»	Kazakhstan
8	Tetyana Khan	ITPCru	Russia
9	Denis Godlevskiy	ITPCru	Russia
10	Natalia Egorova	ITPCru	Russia
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12	Meruert Bektemisova	“Partnership network” Association	Kyrgyzstan
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14	Sergey Uchaev	ISHONCH VA HAYET	Uzbekistan
15	Anatoli Leshanok	RPA“People PLUS”	Belarus
16	Irina Statkevich	BPA "Positive Movement"	Belarus
17	Marina Chokheli	TB People/OSF Georgia	Georgia
18	Zoya Zamihovska	100% LIFE	Ukraine
19	Evgenia Kononchyk	100% LIFE	Ukraine
20	Nadiia Savchenko	100% LIFE	Ukraine
21	Olha Klymenko	TB people UA	Ukraine
22	Mykyta Trofymenko	100% LIFE	Ukraine
23	Anastasiia Homeniuk	100% LIFE	Ukraine
24	Anastasiia Rupcheva	100% LIFE	Ukraine
25	Maryna Kopylenko	100% LIFE	Ukraine
26	Anahit Harutyunyan	“Positive People Armenian Network” Social NGO	Armenia
27	Oleksandra Kolotyha	100% LIFE	Ukraine
28	Morgane Ahmar	ITPC Global	Morocco

Facilitator: Sergey Golovin

Beginning of the meeting. Introduction of participants. One minute's silence in remembrance of people who died before they could receive treatment.

Beginning of presentation

My name is Stephanie Seidel, I represent the organization TB-Alliance (hereinafter – TBA). My colleague, Sarah Cook-Scalise will also be present at this call. Today I will provide information on the work of TBA, on clinical trials and drugs that we invest in. As you know, the drug pretomanid was recently approved, so I will also talk about programs to improve access to the BPaL regimen (bedaquiline + pretomanid + linezolid).

TBA is a non-profit organization founded in 2000 to develop and market new, more effective drugs for the treatment of tuberculosis (TB) with a shorter treatment duration. We are a partnership that develops drugs; we are located in New York and South Africa. We work in close partnership with pharmaceutical companies, research institutes and activists around the world.

We develop new treatment regimens for both drug-sensitive and drug-resistant TB, and our mission is to ensure that the drugs we develop are available on the market and affordable by their price. Our mandate is three A's: Adopted (drugs must be registered and included in treatment programs), Available (drugs with market availability) and Affordable.

Our strategy for the development of drugs is treatment with new, more effective drugs, simplification of regimens and making the duration of treatment shorter. Current treatment for TB takes from 6 to 30 months, while treatment with new drugs takes up to 3-6 months, and the main goal is to treat tuberculosis like any standard bacterial infection (7-10 days).

Our vision: we develop fully oral, effective treatment regimens with a treatment duration of 3 to 6 months; they must be affordable, integrated into treatment policies and physically accessible so that millions of people living with TB are saved. This is only possible in close partnership with other stakeholders, and we have partners around the world, i.e. clinical trial organizations, community-based organizations, donors and partner associations.

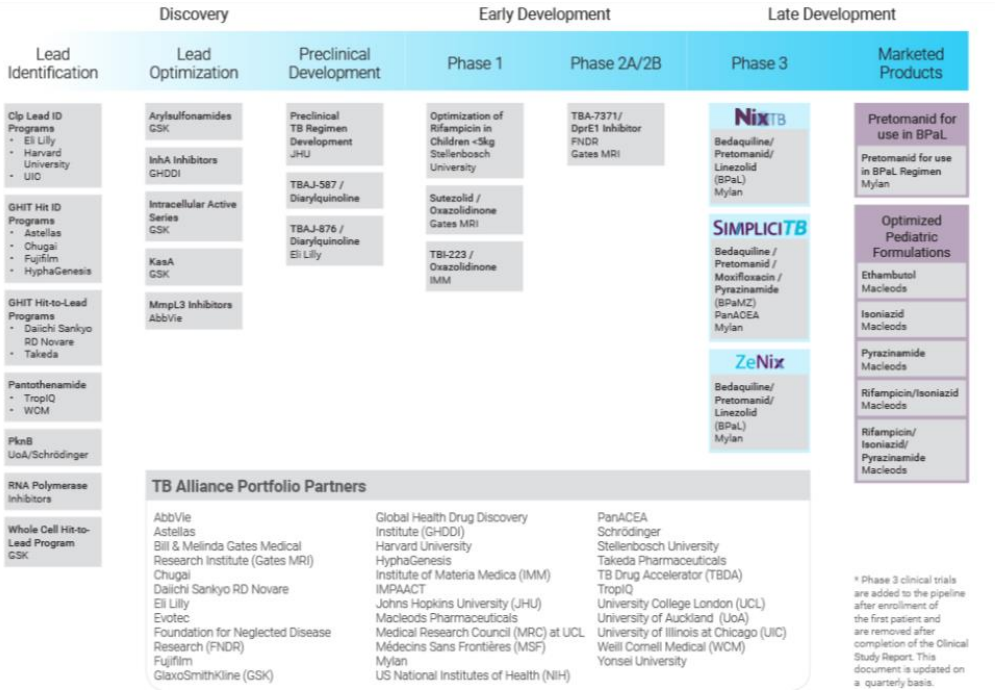
As you already know, TBA received FDA approval for pretomanid as part of a combination regimen that also includes linezolid and bedaquiline. Pretomanid was developed by TBA and was studied in a group of patients with extensively drug-resistant TB (XDR-TB). The basis for the registration dossier was the Nix-TB study. The results of this study demonstrated success for 95 of the first 107 patients after 6 months of treatment with the bedaquiline + pretomanid + linezolid (BPaL) regimen; Nix-TB participants were followed for 24 months after the end of the course of treatment to monitor for long term safety or relapse, I will talk about them a little later.

It is worth noting that pretomanid was approved by the LPAD procedure (a procedure for registering antibacterial and antifungal drugs for limited population groups for which at the time of initiating the clinical trial treatment options available had approximately 20% cure rates – the pre-bedaquiline era).

I will tell you little bit about pretomanid. This is the third FDA registered TB drug in the last 40 years. It belongs to the chemical class known as nitroimidazooxazines. The mechanism of action of the drug is described on the TBA website: www.tballiance.org/pretomanid.

As you know, we have entered into a global commercial agreement with Mylan for pretomanid, as well as for the combinations of BPaL and BPaMZ (bedaquiline + pretomanid + moxifloxacin + pyrazinamide).

Now I will talk about our research and development program. This slide shows the TBA pipeline drugs.



Here are also presented the drugs that are in the very early stages of development (on the left side). I will talk through the clinical programs, NixTB, SimpliciTB and ZeNix, today.

NixTB and BPaL regimen:

There are a number of problems with XDR-TB treatment: high drug load and treatment duration of more than 18 months. The treatment protocols for both XDR-TB and MDR-TB are changing, and over the past few years, with the advent of new drugs, rates have improved even for these complex patients. I will now give information about the BPaL regimen that has been used for 6 months. This three-drug regimen is used to treat pulmonary XDR-TB or MDR-TB patients with drug intolerance or lack of response to treatment. All patients received 200 mg of pretomanid once a day. As for bedaquiline, at first there was a loading dose of bedaquiline for 2 weeks, and then 200 mg three times a week. The initial dose of linezolid was 1200 mg per day with the possibility of decreasing to 600 mg. The study was conducted at 3 sites in South Africa. Initially, we conceived this treatment as a study for patients who did not have other treatment options, it was a salvation regimen. We planned to include up to 200 patients in this study. After completing a six-month course of treatment, patients were observed for another 2 years. Patient enrollment was completed in November 2017. The primary endpoint of the study was 6 months after the completion of treatment and a favorable outcome was a patient with cure of the TB infection and negative sputum cultures. If necessary, the course of treatment could be extended to 9 months.

According to the status of this study (the latest results will be published in the near future) I will share the results that are currently available. 109 patients (all participants) completed the course of treatment. We have the initial results of the analysis of data on the intention-to-treat methodology for the first 75 participants, which were presented at the Union conference last year. Results are as follows: 89% of these 75 patients had a positive result (cured – defined as a sputum negative result after 6 months of treatment and 6 months of follow-up). At the time of the start of the study, according to WHO estimates, the average cure rate for XDR-TB was 34%; in recent years, this indicator has been improved.

This slide shows the data for 107 patients: 89% (95 people) were cured. As you can see, the cure rates remained the same as for the first 75 patients. This was true for both the subgroup of patients with XDR-TB and the subgroup of patients with MDR-TB who did not tolerate or did not respond to MDR-TB treatment. There is a summary of those 12 patients whose treatment failed. If you have questions about

these cases, I can provide more detailed information. There were two relapses after the completion of treatment. One patient died on day 486 of the study. We collect data on whether it was a relapse or reinfection.

We know that in the NixTB study there were problems associated with the high toxicity of the drug, linezolid. In this regard, an additional dose-ranging study was conducted, the purpose of which was to establish the optimal dosage of linezolid. The dosages studied were from 300 mg to 1200 mg. The efficacy of the drug was studied at various doses. The slide shows the different dosages of linezolid (300 mg once a day, 300 mg twice a day, 60 mg once a day, 600 mg twice a day, 1200 mg once a day). The outcomes of this study form the basis for the linezolid doses being studied in the ZeNix-TB trial.

The following slide shows the ZeNix study. It studies the same regimen as the Nix-TB study (bedaquiline, pretomanid, and linezolid), however with two randomized arms using lower dose of linezolid, and a shorter duration of linezolid. In this study, we are trying to understand how much we can reduce the dosage of linezolid, as well as reduce the course of treatment. As part of this study, we also look at the possibility of optimizing the dosage of bedaquiline. Patient enrollment for this study is currently underway in Georgia, South Africa, Russia and Moldova.

This study will include the same categories of patients (XDR-TB or MDR-TB with drug intolerance or lack of response to treatment), as well as pre-XDR patients, for treatment with BPaL. There will be 4 groups in this study, and as mentioned earlier, we strive to simplify the regimen and do not use a loading dose of bedaquiline at the start, but use a dosage of 200 mg throughout.

In the first two groups we use the same dosage of linezolid that was in the first study (1200 mg once a day) for 6 months and 2 months. In two other groups, a 600 mg linezolid daily regimen will be studied for 6 months and 2 months. The dosage of bedaquiline is 200 mg for 8 weeks, then 100 mg for 18 weeks. We hope that the efficacy will be comparable with the results of the NixTB study, but the toxicity of the regimen will be reduced due to the fact that we are reducing the dosage of linezolid.

At this stage, we have enrolled 139 patients. We have one site in Georgia, one in Moldova, and four sites both in Russia and South Africa.

Question: Are you planning to expand the list of countries?

Answer: At the moment, we plan to use those sites that have already been included, and to enroll 200 patients.

Question: Do studies in these countries comply with good clinical practice standards or protocols of WHO and other regulatory authorities?

Answer: Yes, the research is conducted as part of the requirements of good clinical practice and good laboratory practice.

Question: You did not mention that there were any control groups in these studies. Were there any comparison groups?

Answer: In the ZeNix study, we compare the results with the NixTB group from the previous study. In fact, the first group (1200 mg of linezolid for 6 months), this is the comparison group that was in NixTB. There was no comparator arm in NixTB - with the current standard of treatment - since at the time this study began, we believed that for ethical reasons, patients should not be given a regimen for treatment of XDR-TB with such low cure rates that was available at that time. This approach has been approved by regulators and many experts. Comparing the data that we have on the NixTB study with the current XDR-TB treatment regimens, we see that the cure rates are significantly higher compared to other currently available regimens.

Question: There is evidence that the regimen is poorly tolerated by people with co-infections of HIV and hepatitis. Can you provide more information on how this manifested itself, what side effects and when can improvement be expected?

Answer: If you mean co-infection with HIV, then within the framework of these studies, the goal was to enroll 50% of patients with co-infection with HIV. Within NixTB, HIV coinfected participants were cured at the same rate as non-HIV coinfected participants. Our overall strategy for improving tolerability is to reduce linezolid dosage for all categories of patients, not only for patients with co-infection. I cannot completely agree that tolerance in patients with co-infection was significantly worse. To our knowledge, the BPaL regimen can be used with dolutegravir, and there are currently no known interactions with ARVs. The only switch from regimen to regimen was associated with bedaquiline, because it cannot be combined with efavirenz.

Question: Will you have detailed information about which ARV therapy regimen the patients received in the study? Will this information be included in the final report? The second question is whether patients with hepatitis C were included and did they receive antiviral drugs and were there any drug interactions with drugs for the treatment of hepatitis C?

Answer: Answering the first part of the question, yes, there is such information, it will be available publicly. Regarding hepatitis C, at the moment I do not have this information, but we can send it later, including criteria for including patients with HCV. Regarding the inclusion of patients in hepatitis C, I think that this will depend not so much on the presence or absence of hepatitis C, but on the degree of liver damage.

Follow-up Answer: We did not test for hepatitis antibodies at screening so we did not know how many patients had Hep C chronic infection during the study, however based on what is known about drug-drug interactions we do not see any problem with treating for Hep C while a patient is receiving the regimen. We routinely test this at screening going forward, including for the SimpliciTB trial.

Another study, the SimpliciTB study, is for both drug-sensitive and drug-resistant tuberculosis. This is a fully oral regimen that includes bedaquiline, pretomanid, moxifloxacin, and pyrazinamide (BPaMZ). For drug-sensitive tuberculosis, we evaluate the effectiveness of the treatment regimen for 4 months compared to the 6-month treatment regimen of the current standard of treatment (isoniazid, rifampicin, pyrazinamide and ethambutol (HRZE)). We also evaluate the safety, tolerability and effectiveness of a 6-month course of treatment with BPaMZ in patients with drug-resistant TB. This study is conducted on 27 sites in 8 countries on 4 continents (Brazil, Georgia, Russia, South Africa, Uganda and Tanzania, as well as Asia).

Study design: This is a partially blinded study, with patients randomized into two groups. Two groups with drug-sensitive tuberculosis are compared: one receives the BPaMZ regimen for 4 months, the other receives a treatment standard, and the HRZE regimen for 6 months. The drug-resistant group TB receives one regimen (BPaMZ) for 6 months.

We already had the NC-005 study; which was a Phase 2 study that evaluated the effectiveness of this regimen in these groups of patients for 8 weeks. In this study, we evaluated different ways of combining bedaquiline and pretomanid, the data on it has been accepted by a journal and will be published imminently. As part of this study, we saw a statistically significant difference when using this regimen in patients with TB drug-resistant (96%), which is significantly higher than with current standard treatment. In fact, the data from this study formed the basis for the design of the SimpliciTB study. We did an interim analysis in TB drug-resistant groups in the SimpliciTB study, and we expect patient enrollment for this study to complete before the end of this year.

Drug Access Issues

We work with different stakeholders who are responsible for the policy and inclusion of new drugs in treatment recommendations, both internationally and nationally. We conduct studies that are designed to show the added value of new drugs, as well as their cost-effectiveness. We also work with suppliers, e.g., Mylan, so that the drug is available to patients, and so that there are supplies.

These are the steps that the organization takes to make the drug available to patients:

- Inclusion in WHO treatment protocols.
- Inclusion in national treatment protocols, especially in countries with high burden of disease.
- Mylan is working to ensure that this regimen is included in the GDF directory.
- In countries where this is possible, Mylan is working to register the drug or obtain special permission to import the drug, including using the GDF mechanisms.
- We understand that the drug must be affordable, and in partnership with Mylan, we negotiated with a large number of stakeholders in order to develop the most acceptable price policy.
- Financing issues are crucial for the product to be used and procured.
- We work with a large number of donors to resolve the issue of financing, one way or another. In particular, we work with the Development Agency in South Korea (Korean Development Agency). There is also TB Reach organization. We also communicate with a large number of organizations, including patient organizations.

I would like to separately show the areas of responsibility of TBA and Mylan.

TBA is responsible for generating and submitting clinical and non-clinical data on the drug to WHO and involving such stakeholders as WHO, Stop TB, Global Fund, USAID. TBA is also responsible for advocacy at the country level, including those aimed at those organizations that will be the first to use the drug, and we focus primarily on countries with high TB prevalence. We also collaborated in countries in the region to develop plans for introducing the transition to this drug. We are trying to play the role of an "independent broker", meaning that thanks to our work, a market for TB treatment regimens is formed.

Mylan responsibilities are as follows: the company is responsible for the prequalification by WHO and the submission of registration dossiers, with the exception of the FDA and EMA, for which TB Alliance is responsible. Mylan will work on demand generation and advocacy at the country level, and will be responsible for the drug access program prior to registration. The company is also responsible for all tenders and price negotiations, production and distribution of pretomanid.

The next slide is about updates to WHO recommendations. We expect that the revised protocols will be published in the first quarter of 2020, in February or March. In the near future, we will submit our dossier to the expert group, including an analysis of efficiency in terms of cost and affordability. All clinical data has already been submitted. During the assessment, WHO will look at all the data ever available. We expect the meeting of the expert group on data assessment will take place in November.

Question: The development of the drug was funded by various humanitarian sources, but only one company was issued a production license. Why was the exclusive license issued?

Answer: In most countries, Mylan's license is not exclusive. The license exclusivity applies primarily to the USA and the EU. We also conclude a distribution license that covers most countries. Both Mylan and we believe that access to generics is very important for the accessibility and lower prices. Mylan will be the first supplier, but we expect that there will be 2-3 more suppliers globally, and, possibly, there will be more suppliers at the regional level.

Question: The question was not so much about the suppliers as about the manufacturers of this drug.

Answer: This applies to both manufacturers and suppliers of the drug.

Question: TBA talked about collaborating with patient groups and activists. In fact, most TB activists are not involved in communication with TBA. The question is, how does this collaboration take place in practice?

Answer: You are right; the TBA initially involved the community in the clinical trial process where it was conducted. At the global level, we talked with selected TB activists, mainly from TBCAB, which is coordinated by the Treatment Action Group. In fact, we are very interested in expanding such cooperation, and we really want to work with a large number of activists in those countries where we want to implement the BPaL regimen. We are now looking for partners in countries that can form part of the advisory groups in countries where the BPaL regimen will be launched. We will also engage in a broad dialogue with various stakeholders, including with the involvement of our partners, Mylan and possibly Janssen. We are grateful for the opportunity to participate in this meeting, and we hope that this interaction at the regional level will continue. In Ukraine, the TB Reach project was recently approved, information on this is on our website, and we will work there with the Danish Tuberculosis Fund and PATH. We can send more detailed information later.

Question: You mentioned that there would be other companies that would have rights for pretomanid. Please tell us, how soon can this be in our region? We are worried that the rights will belong to a monopolist, and we will not have the drug in the region.

Answer: That is a good question. We are now at the final stage of negotiations with one company, which are about to finish.

Question: Our region is one of the most affected by tuberculosis. New drugs and regimens are very important in terms of the fact that these are fewer tablets and shorter courses of treatment, but in order not to face the issue of adherence to treatment in the future, it is important to have full information about the drug, about quality, side effects, risks, and properly present this information to patients so that there are no myths and patients' resistance to treatment. This is a request for the receipt and distribution of detailed information about the drug and this treatment regimen.

Answer: We absolutely agree with you. We are now working on the development of training materials on the use of this regimen, which will be finalized in the near future and will be available to doctors and medical personnel.

Comment: It is very important that these materials also contain information about the inter-drug interaction with ARV drugs, drugs for the treatment of hepatitis C and opioid replacement therapy, etc.

Answer: Yes, of course, this information will be included.

Comment of Mylan representative: As we have already said, the cost of pretomanid treatment course will be about $400.

Follow-up comment: On October 28, the GDF announced a price of $364 for 6 months of pretomanid as part of the BPaL regimen.

End of the meeting.