BPaL Operational Research: Experience of Ukraine

Natalia Litvinenko,

Doctor of Medical Sciences, Head of the Research Center for DR TB

OR Principal Investigator

SF National Institute of Phthisiology and Pulmonology n.a. Yanovsky NAMSU

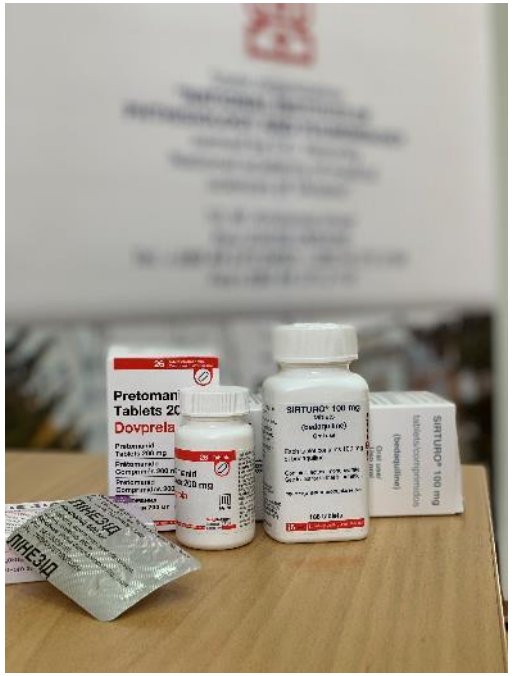
Pretomanid

Pretomanid – the third new anti-TB drug approved by the USA FDA after rifapentine and bedaquiline

- Pretomanid is a new anti-TB drug developed and registered by a non-profit organization
- Approved as part of the standard regimen
- First standard regimen after HRZE

Benefits of BPaL Regimen:

1. **Short:** *6-month regimen, few treatment defaults*
2. **Intake of only 5! pills a day:** *3 types of pills*
3. **High efficacy:** *cure rate more than 90%*
4. **Low cost:** *cost per treatment – $ 364*
5. **Manageable tolerability:** *SAE – 17% according to the research*



What is implemented in Ukraine?

- Implementation of BPaL - within the framework of the **OR Pilot Study to Assess Efficacy and Safety of Antimicobacterial Therapy with BPaL Regimen in Ukraine.**
- **The OR is conducted on the basis of the NIPP NAMSU within the framework of Development of the Evidence Base for the Introduction of Latest Shorter Treatment Regimens for Drug-resistant Tuberculosis in Ukraine project (project director-Yuriy Gamazin**), it is implemented by the Charity Foundation Organization of Optimal Technologies in Healthcare (OATH)
- **Technical support of the project** - international organization Tuberculosis Foundation (KNCV), the Netherlands
- **The project is funded by** the Stop TB Partnership (Geneva, Switzerland) through the TB REACH Special Initiative and the United Nations Office for Project Services (UNOPS).
- **Project's partners**: Support TB project, implemented by PATH with funding from USAID

Research Team:

Principal investigator:

Litvinenko Natalia, *doctor of medical sciences, head of the Research Center for DR TB NIPP NAMSU, OATH*

Team members:

Gamazin Yuriy, *project director BPaL/Ukraine, OATH*

Pogrebnaya Marina, *PhD, SRF Research Center for DR TB NIPP NAMSU– coordinator of the OR;*

Senko Yulia, *PhD, SRF Research Center for DR TB NIPP NAMSU – psychological support officer;*

Lafeta Anastasia, *JRF Research Center for DR TB NIPP NAMSU – OR monitoring officer;*

Mirtskhulava Veriko, *PhD, senior epidemiologist, Tuberculosis Foundation KNCV;*

Terleeva Yana, *NTP manager, CPH MoH Ukraine.*

OR Objectives

Primary

- Determine the treatment efficacy at the time of treatment completion
- Assess safety based on the incidence of serious adverse events (SAE)

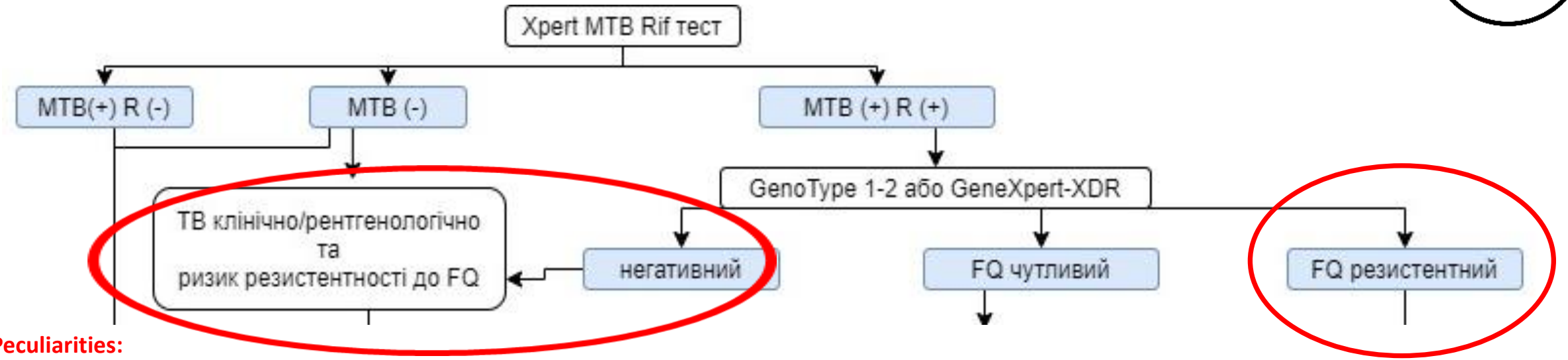
Secondary

- Determine the time to culture conversion
- Determine the percentage of relapse-free patients 6 and 12 months after the successful treatment completion
- Identify the rate of clinically significant adverse events:
  - *QT interval prolongation*
  - *peripheral neuropathy*
  - *myelosuppression*
  - *optic neuritis*
  - *hepatotoxicity*

Sample Size

- 135 patients to be enrolled in BPaL regimen within the OR

Evaluation of laboratory diagnosis results



Peculiarities:

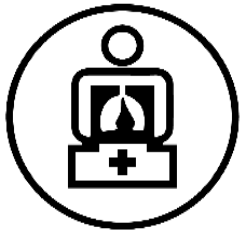
New cases/TB relapses:

- GenoType - FQ resistant – consider enrollment in BPaL regimen (not waiting for pDST result!)
- GenoType negative/not done + confirmed close contact with QT-resistant TB - consider enrollment in BPaL regimen (not waiting for pDST result!))
- GenoType negative /not done + non-verified contact with QT-resistant TB – treatment with mSTR or waiting list (ITR – is not advisable!!!)

Repeated MDR-TB / XDR / TB:

- *Additionally: we study the history of previous treatment (those treated with Bdq Lzd Dlm <4 weeks, had treatment failure or intolerance at previous stages) - consider enrolment in BPaL (regardless of gDST and pDST)*
- *Test results- from no more than 3 months ago (if the patient was waiting for treatment)*

Changes in the Inclusion/Exclusion Criteria During the Study



Study Screening Form (Part I)

Country	Ukraine
Name of DR-TB treament center	NIPP
Study site	0 0 1
Study screening date	4/7/21 dd/mm/yyyy

Patient Information

Study Number	
DR-TB Registration Number	3 1 7 7 5 8 - 2
Patient initials	Y V O
Sex	2-Female
Date of birth[1]	10/31/88 Age 32

Patient ID 0 0 1 - [ ] - 3 1 7 7 5 8 - 2
Study site *Study number* *DR-TB number*

A. Inclusion criteria

1	Has the patient had laboratory-confirmed (rapid and/or conventional DST) resistant TB to at least rifampicin and fluoroquinolones within the **last three months*** of the screening date?	1-Yes
2	Has the patient had strong clinical and radiological evidence of active TB **and** has the patient been a close household contact of an index patient with active laboratory-confirmed resistant TB to at least **Rifampicin** and **Fluoroquinolones** and no documented resistance to any of the BPaL component drugs (Bedaquiline, Pretomanid, Linezolid) within the **last three months*** of the screening date?	2-No
	Questions for previously treated patients only	
3	Has the patient documented MDR/RR-TB treatment non-response[2] and bacteriologically confirmed active TB within the **last three months*** of the screening date?	2-No
4	Has the patient documented intolerance[3] to MDR-/RR-TB treatment and bacteriologically confirmed active TB within the **last three months*** of the screening date?	2-No

*If none of the questions above is answered **YES**, the patient does not meet the inclusion criteria*

Go to Section E

* Otherwise Xpert testing and 2nd line LPA must be done for patient before enrollment in the study.

** Answer **Unknown** is acceptable only if the patient is a close household contact of an index patient with active laboratory-confirmed resistant TB to at least RIF and FQ and no documented resistance to any of the BPaL component drugs (Bedaquiline, Pretomanid, Linezolid) within the last 3 months* of the screening date

*** Answer **Unknown** is acceptable only if the patient had laboratory-confirmed (rapid and/or conventional DST) resistant TB to at least RIF and FQ within the last 3 months* of the screening date

[1] If less <15 years of age patient does not meet the eligibility criteria; if >15 and <18 years old, patient should be evaluated by the Expert Committee enrollment in the study.

[2] Non-response is defined as:
a) two consecutive positive cultures of sputum samples collected after the end of the 2nd month (separated by 30 days) of treatment with lack of clinical improvement or deterioration
b) treatment outcome of "failure" according to the WHO definition

[3] Intolerance is defined as: Inability to continue the second-line MDR-/RR-TB regimen due to a documented intolerance to any of the component drugs

Study Screening Form (Part II)

Study screening date (from part I) 4/7/21 dd/mm/yyyy

Patient ID 0 0 1 - [ ] - 3 1 7 7 5 8 - 2
(from part 1) *Study site* *Study number* *DR-TB number*

B. Exclusion criteria

1	Does the patient have a known previous exposure to any of the BPaL component drugs (Bedaquiline, Pretomanid, Linezolid) or Delamanid for **>4 weeks**?	2-No
2	Does the patient's DST show infection with a strain resistant to any of the BPaL component drugs (Bedaquiline, Pretomanid, Linezolid)?	2-No
3	Does the patient have a known allergy to any of the BPaL component drugs (Bedaquiline, Pretomanid, Linezolid)?	2-No
4	Does the patient have a known severe adverse event associated to any of the BPaL component drugs (Bedaquiline, Pretomanid, Linezolid)?	2-No
5	Does the patient have a form of extrapulmonary TB that would require treatment longer than would be usual for pulmonary TB (e.g. TB meningitis, other central nervous system TB, or TB osteomyelitis)?	2-No
6	Is the patient unable to take oral medication?	2-No
7	Does the Patient weight <35 kg?	2-No
	Questions for <55-year-old woman only	
8	Is patient pregnant?	
9	Pregnancy test result:	2-negative
	< 55-year-old woman must do the pregnancy test before starting the BPaL treatment regimen	
10	Is the patient reluctant to use effective contraception while on the BPaL treat.?	2-No
11	Is the patient breastfeeding?	2-No

*If all questions are answered **NO** and patient has a negative pregnancy test, **go to Section C***

*If any question is answered **YES** or patient has a positive pregnancy test, the patient does not meet the eligibility criteria. **Go to Section E**.*

C. Relative contra-indications

1	Does patient have baseline QTcF ≥ 500ms? [4]	2-No
2	Does patient have hemoglobin level < 8.0 g/dL (80.0 g/L)?	2-No
3	Does patient have severe peripheral neuropathy? [5]	2-No
4	Does patient have AST/ALT > 3 times the upper limit of normal?	2-No
5	Does patient have serum creatinine > 3 times the upper limit of normal?	2-No

*If all questions are answered **NO** in Sections C, **go to Section D***

*If any question is answered **YES**, patient should be evaluated by the Expert Committee.*

*The **Expert Committee** should make decision about the patient's **enrollment** in the study*

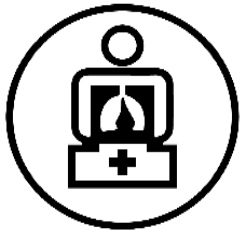
6	Has the Expert Committee decided to enroll the patient in the study?	1-Yes

If Yes, go to **Section D** If No, go to **Section E**

[4] Fredericia Corrected QT Interval enrollment in the study.

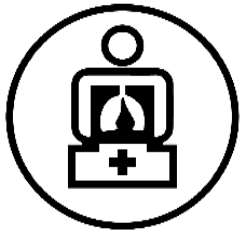
[5] Brief Peripheral Neuropathy Screen developed and validated by the National Institutes of Health, funded AIDS Clinical Trials Group

OR Patient Enrolment Cascade: Screening



- Have been screened or are at the screening stage – 69 people:
  - Excluded during screening or further examination prior to the onset of treatment – 8 people:
    - ✓ *Previously treated – 3*
    - ✓ *Drug resistant to Linezolid – 1*
    - ✓ *Opting out – 1*
    - ✓ *Polyneuropathy, anemia prior to treatment – 1*
    - ✓ *Decompensated DM, ALT*
    - ✓ *Drug susceptibility to fluoroquinolones*
  - At the screening stage – 2 people
- In total, 59 people were enrolled and started treatment

OR Patient Enrollment Cascade: Enrollment



- Enrolled and started treatment: 59 people
- Excluded during treatment– 6 people:
  - ✓*Died (5 grade) - 1*
  - ✓*Stomach ulcer complicated by bleeding (4 grade) - 1*
  - ✓*Hepatotoxicity (4 grade) - 1*
  - ✓*Opting out (in 2 weeks) - 1*
  - ✓*Drug resistance to linezolid (pDST) – 2*
- In total, 53 people are currently on treatment

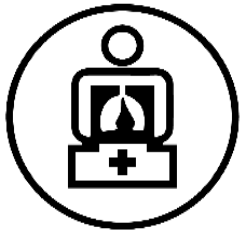
Adverse Events:

- At least 1 AE– 27 people
- More than 1 AE– 6 people
- 3-4 grade AE (SAE) – 11 people
  - Excluded from BPaL because of AE – 3 people
  - Continue treatment after the resolution of the AE – 9 people

Types of AE:

Type	Total number	Grade 3-4
• Complicated epididymitis	1	1
• AF	1	1
• Hepatotoxicity	7	5
• Hypoalbuminemia	1	0
• Elevated creatinine	1	0
• Insomnia	2	0
• Myelosuppression	16	4
• Pancreatitis	1	4-5
• Polyneuropathy	2	1
• Gastric ulcer (hemorrhage)	1	1
• Dry mouth	1	0
• Nephrotoxicity	1	0
• Ovarian apoplexy	1	1

Time of AE

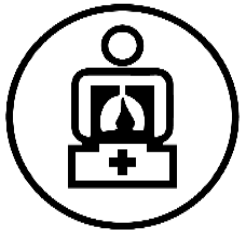


Type of AE	2 weeks	1 month	2 months	3 months	4 months	5 months	6 months	Total
Hepatotoxicity	2	3	1		1	-	-	7
Myelosuppression	2	9	2	1	2	-	-	16

AE Management

- Discontinuation of treatment – up to 2 weeks in the first month of treatment and up to 35 days after the first month of treatment
- If treatment needs to be discontinued several times, the total duration of discontinuation should not exceed 35 days
- Following the discontinuation of treatment in the first month of treatment – linezolid is prescribed continuously at a dose of 1.2 g for at least 4 weeks
- Linezolid-associated AEs: it is possible to reduce the dose to 600 mg, 300 mg or completely discontinue it (after the 1st month of treatment)

AE Management

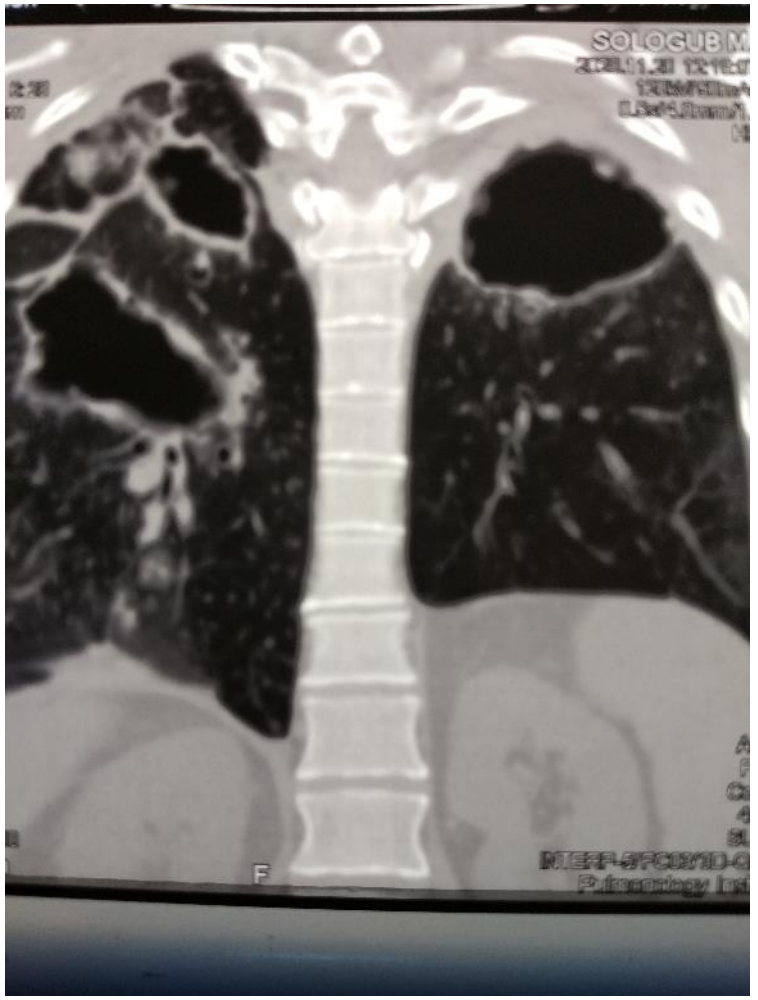


Type of AE	1-2 grade	3-4 grade	Temporary Discontinuation of treatment	Complete discontinuation of treatment	No treatment regimen changes	Linezolid dose reduction to 600 mg	Linezolid dose reduction to 300 mg
Hepatotoxicity	2	5	5	1	1	-	-
Myelosuppression	12	4	8	0	3	2	3

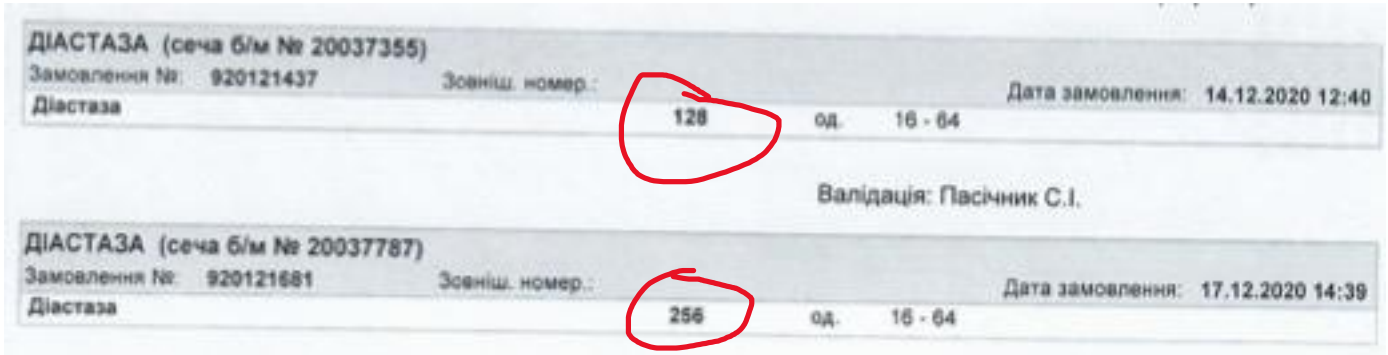
Patient 015

- Male, 40 years old
- Previously treated XDR-TB (2011)
- Poorly curable process,
- 3 degree respiratory distress - SpO2 concentration – to 70 without oxygen support

- Start of treatment 4.12.2020



Patient 015



ДІАСТАЗА (сеча б/м № 20037355)

Замовлення №: 920121437 Зовніш. номер.: Дата замовлення: 14.12.2020 12:40

Діастаза 128 од. 16 - 64

Валідація: Пасічник С.І.

ДІАСТАЗА (сеча б/м № 20037787)

Замовлення №: 920121681 Зовніш. номер.: Дата замовлення: 17.12.2020 14:39

Діастаза 256 од. 16 - 64

	23.11.2020 12:49:23	04.12.2020 11:15:45	04.12.2020 11:18:50	15.12.2020 10:47:05	15.12.2020 10:57:27
Бактерії				в незначній кількості міцелій грибків	міцелій гр. -небагато
Епітелій перехідний		поодинокий у полі зору	поодинокий у полі зору	поодинокий у препараті	поодинокий у препараті
Епітелій плаский		поодинокий у препараті	поодинокий у полі зору	у незначній кількості	у незначній кількості
Еритроцити змінені					
Еритроцити малозмінені		близько 5 в п/зр.	до 5		
Еритроцити незмінені				5-7-12 в п/зр.	5-7-12
Колір		солом'яно-жовтий		жовтий	
Лейкоцити		0-3 в п/зр.	0-3	6-8 в п/зр.	6-8
Микроскопія осаду сечі					
Прозорість		прозора		мутна	
Слиз		в незначній кількості	в незначній кількості	в помірній кількості	в помірній кількості
Солі					
Солі оксалату		поодинокі у полі зору	поодинокі у полі зору оксал.		
Солі урати				у дуже великій кількості	у дуже великій кількості урати
Циліндри					
Циліндри гіалінові				поодинокі у препараті	поодинокі у препараті
Циліндри епітеліальні					
Циліндрі лейкоцитарні					
аскорбінова кислота	відсутня	відсутня		відсутня	
білок	відсутній	відсутній		+++3,0 (2.0-5.0 г	
білірубін	негативний	негативний		негативний	
глюкоза	відсутня	відсутня		відсутня	
загальний аналіз сечі (суха хімія)					
кетони	відсутні	відсутні		1+(15)	
кислотність	6.0	5.5		6.0	
кров	негативний (еритроцити відсутні або поодинокі у препараті)				
лейкоцити	відсутні (відсутні-поодинокі у полі зору)				
нітрити	відсутні	відсутні		відсутні	
питома вага	1.020	1.020		1.025	

- Pancreatitis, nephrotoxic syndrome
- Management: intensive therapy

Acknowledgement:

1. CPH MoH Ukraine
2. Administration of the Institute and the Research Team
3. Regional TB facilities of Ukraine
4. Development of Evidence Base for the Introduction of the Latest Shorter Treatment Regimens for Drug-resistant Tuberculosis in Ukraine project (project director - Yuriy Gamazin) implemented by the Charity Foundation Organization of Optimal Technologies in Healthcare (OATH)
5. Tuberculosis Foundation KNCV, the Netherlands
6. Stop TB Partnership (Geneva, Switzerland, TB REACH Initiative, United Nations Office for Project Services (UNOPS)
7. Support TB Project, implemented by PATH with the USAID funding
8. WHO

Thank you for your attention!