

PROGRAMME AND METHODOLOGY
of Cohort Event Monitoring
of BEDAQUILINE safety and effectiveness
in combination antituberculosis therapy

No 1-Bdq of 05 May 2015

APPROVED

Director of the Republican Scientific
and Practical Center for Pulmonology
and Tuberculosis

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and Tuberculosis

_____ 2015
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1. General information

Programme title: Cohort Event Monitoring of Bedaquiline safety and effectiveness in combination antituberculosis therapy of patients with pre-XDR / XDR-TB

Programme number: No 1-Bdq of 05.05.2015

Monitoring clinical sites:

1. Republican Scientific and Practical Center for Pulmonology and Tuberculosis
2. Minsk oblast TB dispensary
3. Grodno oblast TB dispensary
4. Gomel oblast TB dispensary
5. Brest oblast TB dispensary
6. Mogilev oblast TB dispensary
7. Vitebsk oblast TB dispensary

CEM responsible specialists:

1. Skrahina Alena
2. Setkina Sviatlana
3. Vetushko Dzmitry
4. Solodovnikova Varvara

Period of CEM performing: not less than 28 months.

2. Information about monitored medicine.

INN – Bedaquiline fumarate.

Trade name of the medicinal product

SIRTURO 100 mg tablets

Qualitative and quantitative composition

Each tablet contains bedaquiline fumarate equivalent to 100 mg of bedaquiline.

Excipient with known effect: Each tablet contains 145 mg of lactose (as monohydrate).

For the full list of excipients, see section “List of excipients”.

Pharmacological properties

- **Pharmacodynamic properties**

Pharmacotherapeutic group: Antimycobacterials, drugs for treatment of tuberculosis, ATC code: J04AK05

Mechanism of action

Bedaquiline is a diarylquinoline. Bedaquiline specifically inhibits mycobacterial ATP (adenosine 5'-triphosphate) synthase, an essential enzyme for the generation of energy in *Mycobacterium tuberculosis*. The inhibition of ATP synthase leads to bactericidal effects for both replicating and non-replicating tubercle bacilli.

Pharmacodynamic effects

Bedaquiline has activity against *Mycobacterium tuberculosis* with a minimal inhibitory concentration (MIC) for drug-sensitive as well as drug-resistant strains (multi-drug resistant including pre-extensively drug resistant strains, extensively drug resistant strains) in the range ≤ 0.008 -0.12 $\mu\text{g/ml}$. The *N*-monodesmethyl metabolite (M2) is not thought to contribute significantly to clinical efficacy given its lower average exposure (23% to 31%) in humans and lower antimycobacterial activity (3- to 6-fold lower) compared to the parent compound.

The intracellular bactericidal activity of bedaquiline in primary peritoneal macrophages and in a macrophage-like cell line was greater than its extracellular activity. Bedaquiline is also bactericidal against dormant (non-replicating) tubercle bacilli. In the mouse model for TB infection, bedaquiline has demonstrated bactericidal and sterilizing activities.

Bedaquiline is bacteriostatic for many non-tuberculous mycobacterial species. *Mycobacterium xenopi*, *Mycobacterium novocastrense*, *Mycobacterium shimoidei* and non-mycobacterial species are considered inherently resistant to bedaquiline.

Pharmacokinetic/pharmacodynamic relationship

Within the concentration range achieved with the therapeutic dose, no pharmacokinetic/pharmacodynamic relationship was observed in patients.

Mechanisms of resistance

Mycobacterial resistance mechanisms that affect bedaquiline include modification of the *atpE* target gene. Not all isolates with high MICs have mutations in the *atpE* gene, suggesting the existence of at least one other mechanism of resistance. Isolates with decreased susceptibility to bedaquiline tend to be less susceptible to clofazimine.

Susceptibility testing breakpoints

When available, the clinical microbiology laboratory should provide the physician with the results of *in vitro* susceptibility test results for antimicrobial medicinal products used in resident hospitals as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting a combination of antibacterial medicinal products for treatment.

Breakpoints

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Minimal inhibitory concentration (MIC) breakpoints are as follows:

Epidemiological Cut-Off (ECOFF) 0.25 mg/l

Clinical Breakpoints S ≤ 0.25 mg/l; R > 0.25 mg/l

S = susceptible

R = resistant

Commonly susceptible species

Mycobacterium tuberculosis

Inherently resistant organisms

Mycobacterium xenopi

Mycobacterium novocastrense

Mycobacterium shimoidei

Non-mycobacterial species

Clinical efficacy and safety

The following definitions applies for resistance categories used:

Multi-drug resistant *Mycobacterium tuberculosis* (MDR_{H&R}-TB): isolate resistant to at least isoniazid and rifampicin, but susceptible to fluoroquinolones and second line injectable agents.

Pre-extensively drug resistant tuberculosis (pre-XDR-TB): isolate resistant to isoniazid, rifampicin, and *either* any fluoroquinolone *or* at least one second line injectable agent (but not to both a fluoroquinolone and a second line injectable agent).

Extensively drug resistant tuberculosis (XDR-TB): isolate resistant to isoniazid, rifampicin, any fluoroquinolone, and at least one second line injectable agent.

A Phase IIb, placebo-controlled, double-blind, randomised trial (C208) evaluated the antibacterial activity, safety, and tolerability of SIRTURO in newly diagnosed patients with sputum smear-positive pulmonary MDR_{H&R}- and pre-XDR-TB. Patients received SIRTURO (n = 79) or placebo (n = 81) for 24 weeks, both in combination with a preferred 5-drug background regimen (BR) consisting of ethionamide, kanamycin, pyrazinamide, ofloxacin, and cycloserine/terizidone. After the 24-week investigational period, the background regimen was continued to complete 18 to 24 months of total multi-drug resistant *Mycobacterium tuberculosis* treatment. A final evaluation was conducted at Week 120. Main demographics were as follows: 63.1% were males, median age 34 years, 35% were Black, and 15% were HIV positive. Cavitation in one lung was seen in 58% of patients, and in both lungs in 16%. For patients with full characterisation of resistance status, 76% (84/111) were infected with anMDR_{H&R}-TB strain and 24% (27/111) with a pre-XDR-TB strain.

SIRTURO was administered as 400 mg once daily for the first 2 weeks, and as 200 mg 3 times/week for the following 22 weeks.

The primary outcome parameter was the time to sputum culture conversion (i.e. the interval between the first SIRTURO intake and the first of two consecutive negative liquid cultures from sputum collected at least 25 days apart) during treatment with SIRTURO or placebo (median time to conversion was 83 days for the SIRTURO group, 125 days for the placebo group (hazard ratio, 95% CI: 2.44 [1.57; 3.80]), p < 0.0001).

In the SIRTURO group, no or only minor differences in time to culture conversion and culture conversion rates were observed between patients with pre-XDR-TB and patients with MDR_{H&R}-TB.

Response rates at week 24 and week 120 (i.e. around 6 months after stopping all therapy) are presented in table 1

Culture Conversion Status, n (%)	mITT population			
	N	SIRTURO/BR	N	Placebo/BR
Overall responder at Week 24	66	52 (78.8%)	66	38 (57.6%)
Patients with MDR _{H&R} -TB	39	32 (82.1%)	45	28 (62.2%)

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Patients infected with a pre-XDR-TB	15	11 (73.3%)	12	4 (33.3%)
Overall non-responder* at Week 24	66	14 (21.2%)	66	28 (42.4%)
Overall responder at Week 120	66	41 (62.1%)	66	29 (43.9%)
Patients with MDR _{H&R} -TB	39 [#]	27 (69.2%)	46 ^{# §}	20 (43.5%)
Patients infected with pre-XDR-TB	15 [#]	9 (60.0%)	12 [#]	5 (41.7%)
Overall non-responder* at Week 120	66	25 (37.9%)	66	37 (56.1%)
<i>Failure to convert</i>	66	8 (12.1%)	66	15 (22.7%)
<i>Relapse</i> [†]	66	6 (9.1%)	66	10 (15.2%)
<i>Discontinued but converted</i>	66	11 (16.7%)	66	12 (18.2%)

* Patients who died during the trial or discontinued the trial were considered as non-responders.

[†] Relapse was defined in the trial as having a positive sputum culture after or during treatment following prior sputum culture conversion.

[#] Extent of resistance based on central laboratory drug susceptibility testing results was not available for 20 subjects in the mITT population (12 in the SIRTURO group and 8 in the placebo group). These subjects were excluded from the subgroup analysis by extent of resistance of *M tuberculosis* strain.

[§] Central laboratory drug susceptibility testing results became available for one additional placebo subject after the week 24 interim analysis.

Study C209 (ongoing) evaluated the safety, tolerability, and efficacy of 24 weeks treatment with open-label SIRTURO as part of an individualized treatment regimen in 233 patients who were sputum smear positive within 6 months prior to screening. This study included patients of all three resistance categories (MDR_{H&R}-, pre-XDR- and XDR-TB).

The primary efficacy endpoint was the time to sputum culture conversion during treatment with SIRTURO (median 57 days, for 205 patients with sufficient data). At week 24, sputum culture conversion was seen in 163/205 (79.5%) patients. Conversion rates at week 24 were highest (87.1%; 81/93) in patients with MDR_{H&R}-TB, 77.3% (34/44) in pre-XDR-TB patients and lowest (54.1%; 20/37) in XDR-TB patients. Extent of resistance based on central laboratory drug susceptibility testing results was not available for 32 subjects in the mITT population. These subjects were excluded from the subgroup analysis by extent of resistance of *Mycobacterium tuberculosis* strain.

At week 120, sputum culture conversion was seen in 148/205 (72.2%) patients. Conversion rates at week 120 were highest (73.1%; 68/93) in patients with MDR_{H&R}-TB, 70.5% (31/44) in pre-XDR-TB patients and lowest (62.2%; 23/37) in XDR-TB patients.

At both week 24 and week 120, responder rates were higher for patients on 3 or more active substances (*in vitro*) in their background regimen.

Of the 163 patients who were responders at week 24, 139 patients (85.3%) were still responders at week 120. Twenty-four of these 24-week responders (14.7%) were considered non-responders at week 120, of which 19 patients had prematurely discontinued the trial while being culture converted and 5 patients had experienced relapse. Of the 42 patients who were non-responders at week 24, confirmed culture conversion after week 24 (i.e., after bedaquiline dosing ended but the background regimen was continued) occurred in 9 patients (21.4%) and was maintained at week 120.

Paediatric population

- **Pharmacokinetic properties**

The pharmacokinetic properties of bedaquiline have been evaluated in adult healthy subjects and in adult multi-drug resistant tuberculosis-infected patients. Exposure to bedaquiline was lower in multi-drug resistant tuberculosis-infected patients than in healthy subjects.

Absorption

Maximum plasma concentrations (C_{max}) are typically achieved at about 5 hours post-dose. C_{max} and the area under the plasma concentration-time curve (AUC) increased proportionally up to the highest doses studied (700 mg single-dose and once daily 400 mg multiple doses). Administration of bedaquiline with food increased the relative bioavailability by about 2-fold compared to administration under fasted conditions. Therefore, bedaquiline should be taken with food to enhance its oral bioavailability.

Distribution

The plasma protein binding of bedaquiline is > 99.9% in all species tested, including human. The plasma protein binding of the *N*-monodesmethyl metabolite (M2) in humans is at least 99.8%. In animals, bedaquiline and its active *N*-monodesmethyl metabolite (M2) are extensively distributed to most tissues, however, brain uptake was low.

Biotransformation

CYP3A4 was the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2).

In vitro, bedaquiline does not significantly inhibit the activity of any of the CYP450 enzymes tested (CYP1A2, CYP2A6, CYP2C8/9/10, CYP2C19, CYP2D6, CYP2E1, CYP3A4, CYP3A4/5 and CYP4A) and does not induce CYP1A2, CYP2C9 or CYP2C19 activities.

Bedaquiline and M2 were not substrates of P-gp *in vitro*. Bedaquiline was a weak OCT1 substrate *in vitro*, while M2 was not. Bedaquiline was not a substrate of MRP2 and BCRP *in vitro*. Bedaquiline and M2 did not inhibit the transporters P-gp, OATP1B1, OATP1B3, BCRP, OAT1, OAT3, OCT1, OCT2, MATE1 and MATE2 at clinically relevant concentrations *in vitro*.

Elimination

Based on the preclinical studies, the bulk of the administered dose is eliminated in faeces. The urinary excretion of unchanged bedaquiline was < 0.001% of the dose in clinical studies, indicating that renal clearance of unchanged active substance is insignificant. After reaching C_{max} , bedaquiline concentrations decline tri-exponentially. The mean terminal elimination half-life of both bedaquiline and the active *N*-monodesmethyl metabolite (M2) is about 5 months (ranging from 2 to 8 months). This long terminal elimination phase likely reflects slow release of bedaquiline and M2 from peripheral tissues.

Special populations

Hepatic impairment

A single-dose study of SIRTURO in 8 subjects with moderate hepatic impairment (Child-Pugh B) demonstrated exposure to bedaquiline and M2 (AUC_{672h}) was 19% lower compared to healthy subjects. No dose adjustment is deemed necessary in patients with mild or moderate hepatic impairment. Bedaquiline has not been studied in patients with severe hepatic impairment (see section 4.2).

Renal impairment

SIRTURO has mainly been studied in patients with normal renal function. Renal excretion of unchanged bedaquiline is insignificant (< 0.001%).

In a population pharmacokinetic analysis of tuberculosis patients treated with SIRTURO 200 mg three times a week, creatinine clearance (range: 40 to 227 ml/min) was not found to influence the pharmacokinetic parameters of bedaquiline. It is therefore not expected that mild or moderate renal impairment will have a clinically relevant effect on the exposure to bedaquiline. However, in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis, bedaquiline concentrations may be increased due to alteration of active substance absorption, distribution, and metabolism secondary to renal dysfunction.

tion. As bedaquiline is highly bound to plasma proteins, it is unlikely that it will be significantly removed from plasma by haemodialysis or peritoneal dialysis.

Paediatric patients

The pharmacokinetics of SIRTURO in paediatric patients have not been evaluated.

Elderly patients

There is limited clinical data (n = 2) on the use of SIRTURO in tuberculosis patients aged 65 years and older.

In a population pharmacokinetic analysis of tuberculosis patients (age range 18 years to 68 years) treated with SIRTURO age was not found to influence the pharmacokinetics of bedaquiline.

Race

In a population pharmacokinetic analysis of tuberculosis patients treated with SIRTURO, exposure to bedaquiline was found to be lower in Black patients than in patients from other race categories. This low exposure was not considered to be clinically relevant as no clear relationship between exposure to bedaquiline and response has been observed in clinical trials. Furthermore, response rates in patients that completed the bedaquiline treatment period were comparable between different race categories in the clinical trials.

Gender

In a population pharmacokinetic analysis of tuberculosis patients treated with SIRTURO no clinically relevant difference in exposure between men and women were observed.

- **Preclinical safety data**

Animal toxicology studies have been conducted with bedaquiline administration up to 3 months in mice, up to 6 months in rats, and up to 9 months in dogs. The plasma bedaquiline exposure (AUC) in rats and dogs was similar to that observed in humans. Bedaquiline was associated with effects in target organs which included monocytic phagocytic system (MPS), skeletal muscle, liver, stomach, pancreas and heart muscle. All of these toxicities except effects on MPS were monitored clinically. In the MPS of all species, pigment-laden and/or foamy macrophages were also seen in various tissues, consistent with phospholipidosis. The significance of phospholipidosis in humans is unknown. Most of the observed changes occurred after prolonged daily dosing and subsequent increases in plasma and tissue concentrations of the active substance. After treatment cessation, all indications of toxicity exhibited at least partial recovery to good recovery.

In a rat carcinogenicity study, bedaquiline, at the high doses of 20 mg/kg/day in males and 10 mg/kg/day in females, did not induce any treatment-related increases in tumour incidences. Compared to the exposures (AUC) observed in subjects with MDR-TB in the bedaquiline phase II trials, the exposures (AUC) in rats at high doses were similar in males and 2-fold higher in females for bedaquiline, and 3-fold higher in males and 2-fold higher in females for M2.

In vitro and *in vivo* genotoxicity tests indicated that bedaquiline did not have any mutagenic or clastogenic effects.

Bedaquiline had no effects on fertility when evaluated in female rats. Three of 24 male rats treated with high bedaquiline doses failed to produce offspring in the fertility study. Normal spermatogenesis and a normal amount of spermatozoa in the epididymides were noted in these animals. No structural abnormalities in the testes and epididymides were seen after up to 6-months of bedaquiline treatment. No relevant bedaquiline-related effects on developmental toxicity parameters were observed in rats and rabbits. The corresponding plasma exposure (AUC) was 2-fold higher in rats compared to humans. In the rat, no adverse effects were observed in a pre- and post-natal development study at maternal plasma exposure (AUC) similar to humans and exposure in the offspring 3-fold higher than in adult humans. There was no effect of maternal treatment with bedaquiline at any dose level on sexual maturation, behavioural development, mating performance, fertility or reproductive capacity of the F1 generation animals. Body weight decreases in pups were noted in high dose groups during the lactation period after exposure to bedaquiline via milk and were not a con-

sequence of in utero exposure. Concentrations of bedaquiline in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma.

Clinical particulars

• Therapeutic indications

Bedaquiline is indicated for use as part of an appropriate combination regimen for pulmonary multidrug-resistant tuberculosis (MDR-TB) in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability. See sections “Posology and method of administration”, “Special warnings and precaution for use” and “Pharmacodynamic properties”.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

• Posology and method of administration

Treatment with Bedaquiline should be initiated and monitored by a physician experienced in the management of multi-drug resistant *Mycobacterium tuberculosis*.

Bedaquiline should be used in combination with at least three medicinal products to which the patient's isolate has been shown to be susceptible *in vitro*. Treatment with the other agents in the regimen should continue after completion of treatment with Bedaquiline. If *in vitro* testing results are unavailable, treatment may be initiated with Bedaquiline in combination with at least four medicinal products to which the patient's isolate is likely to be susceptible.

It is recommended that Bedaquiline is administered by directly observed therapy (DOT).

Posology

The recommended dosage is:

- Weeks 1-2: 400 mg (4 tablets of 100 mg) **once daily**
- Weeks 3-24: 200 mg (2 tablets of 100 mg) **three times per week** (with at least 48 hours between doses).

The total duration of treatment with Bedaquiline is 24 weeks. Data on longer treatment duration is very limited. In patients with extensive drug resistance, where Bedaquiline is considered necessary beyond 24 weeks to obtain a curative treatment, a longer duration of therapy may be considered only on a case by case basis and under close safety surveillance (see sections “Special warnings and precaution for use” and “Undesirable effects”).

Missed doses

Patients should be advised to take Bedaquiline exactly as prescribed and to complete the full course of therapy.

If a dose is missed during the first two weeks of treatment, patients should not make up the missed dose, but should continue the usual dosing schedule.

If a dose is missed from week three onwards, patients should take the missed dose of 200 mg as soon as possible and then resume the three times a week regimen.

Elderly population (≥ 65 years of age)

There is limited clinical data (n = 2) on the use of Bedaquiline in elderly patients.

Hepatic impairment

No dose adjustment is necessary for Bedaquiline in patients with mild or moderate hepatic impairment (see section “Pharmacodynamic properties”). Bedaquiline should be used with caution in patients with moderate hepatic impairment (see section “Pharmacokinetic properties”). Bedaquiline has not been studied in patients with severe hepatic impairment and is not recommended in this population.

Renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. In patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease requiring haemodialysis or peritoneal dialysis, Bedaquiline should be used with caution (see section “Pharmacokinetic properties”).

Paediatric population

The safety and efficacy of Bedaquiline in children aged < 18 years have not yet been established. No data are available.

Method of administration

Bedaquiline should be taken orally with food, as administration with food increases oral bioavailability by about 2-fold (see section “Pharmacokinetic properties”). Bedaquiline tablets should be swallowed whole with water.

- **Contraindications**

Hypersensitivity to the active substance or to any of the excipients listed in section “List of excipients”.

- **Special warnings and precautions for use**

There are no data on treatment with Bedaquiline longer than 24 weeks within the clinical studies C208 and C209 (see section “Pharmacodynamic properties”).

There are no clinical data on the use of Bedaquiline to treat:

- extra-pulmonary tuberculosis (e.g. central nervous system, bone)
- infections due to mycobacterial species other than *Mycobacterium tuberculosis*
- latent infection with *Mycobacterium tuberculosis*

There are no clinical data on the use of Bedaquiline as part of combination regimens used to treat drug-susceptible *Mycobacterium tuberculosis*.

Mortality

In the 120-week C208 trial where Bedaquiline was administered for 24 weeks in combination with a background regimen, more deaths occurred in the SIRTURO treatment group than in the placebo group (see section 4.8). The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with Bedaquiline treatment. For additional information on deaths in the C209 trial, see section 4.8.

Cardiovascular safety

Bedaquiline prolongs the QTc interval. An electrocardiogram should be obtained before initiation of treatment and at least monthly after starting treatment with bedaquiline. Serum potassium, calcium, and magnesium should be obtained at baseline and corrected if abnormal. Follow-up monitoring of electrolytes should be performed if QT prolongation is detected (see sections “Interaction with other medicinal products and other forms of interaction” and “Undesirable effects”).

When bedaquiline is co-administered with other medicinal products that prolong the QTc interval, an additive or synergistic effect on QT prolongation cannot be excluded (see section “Interaction with other medicinal products and other forms of interaction”). Caution is recommended when prescribing bedaquiline concomitantly with medicinal products with a known risk of QT prolongation. In the event that co-administration of such medicinal products with bedaquiline is necessary, clinical monitoring including frequent electrocardiogram assessment is recommended.

In the event that co-administration of clofazimine with bedaquiline is necessary, clinical monitoring including frequent electrocardiogram assessment is recommended (see section “Interaction with other medicinal products and other forms of interaction”).

SIRTURO treatment initiation is not recommended in patients with the following, unless the benefits of bedaquiline are considered to outweigh the potential risks:

- Heart failure;
- QT interval as corrected by the Fridericia method (QTcF) > 450 ms (confirmed by repeat electrocardiogram);
- A personal or family history of congenital QT prolongation;
- A history of or ongoing hypothyroidism;
- A history of or ongoing bradyarrhythmia;
- A history of Torsade de Pointes;
- Concomitant administration of fluoroquinolone antibiotics that have a potential for significant QT prolongation (i.e., gatifloxacin, moxifloxacin and sparfloxacin).
- Hypokalemia

Bedaquiline treatment must be discontinued if the patient develops:

- Clinically significant ventricular arrhythmia
- A QTcF interval of > 500 ms (confirmed by repeat electrocardiogram).

If syncope occurs, an electrocardiogram should be obtained to detect any QT prolongation.

Hepatic safety

Increases in transaminases or aminotransferase elevations accompanied by total bilirubin $\geq 2x$ ULN were seen in clinical trials during administration of SIRTURO with the background regimen (see section “Undesirable effects”). Patients should be monitored throughout the treatment course, since the increases in liver enzymes were slow to appear and increased gradually during the 24 weeks. Monitor symptoms and laboratory tests (ALT, AST, alkaline phosphatase, and bilirubin) at baseline, monthly while on treatment, and as needed. If AST or ALT exceeds 5 times the upper limit of normal then the regimen should be reviewed and Bedaquiline and/or any hepatotoxic background medicinal product should be discontinued.

Other hepatotoxic medicinal products and alcohol should be avoided while on Bedaquiline, especially in patients with diminished hepatic reserve.

Interactions with other medicinal products

CYP3A4 inducers

Bedaquiline is metabolised by CYP3A4. Co-administration of bedaquiline and medicinal products that induce CYP3A4 may decrease bedaquiline plasma concentrations and reduce its therapeutic effect. Co-administration of bedaquiline and moderate or strong CYP3A4 inducers used systemically should, therefore, be avoided (see section “Interaction with other medicinal products and other forms of interaction”).

CYP3A4 inhibitors

Co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors may increase the systemic exposure to bedaquiline, which could potentially increase the risk of adverse reactions (see section 4.5). Therefore, the combination of bedaquiline and moderate or strong CYP3A4 inhibitors used systemically for more than 14 consecutive days should be avoided. If co-administration is required, more frequent electrocardiogram monitoring and monitoring of transaminases is recommended.

Patients infected with human immunodeficiency virus (HIV)

There are no clinical data on the safety and efficacy of bedaquiline when co-administered with antiretroviral agents.

There are only limited clinical data on the efficacy of bedaquiline in HIV-infected patients not receiving antiretroviral (ARV) therapy. Those patients studied all had CD4+ cell counts greater than 250×10^6 cells/l (N = 22; see section 4.5).

Lactose intolerance and lactase deficiency

Bedaquiline contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

- **Interaction with other medicinal products and other forms of interaction**

The elimination of bedaquiline has not been fully characterised *in vivo*. CYP3A4 is the major CYP isoenzyme involved *in vitro* in the metabolism of bedaquiline and the formation of the *N*-monodesmethyl metabolite (M2). Urinary excretion of bedaquiline is negligible. Bedaquiline and M2 are not substrates or inhibitors of P-glycoprotein.

CYP3A4 inducers

Bedaquiline exposure may be reduced during co-administration with inducers of CYP3A4.

In an interaction study of single-dose bedaquiline and once daily rifampicin (strong inducer) in healthy subjects, the exposure (AUC) to bedaquiline was reduced by 52% [90% CI (-57; -46)]. Due to the possibility of a reduction of the therapeutic effect of bedaquiline due to a decrease in systemic exposure, co-administration of bedaquiline and moderate or strong CYP3A4 inducers (e.g.

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efavirenz, etravirine, rifamycins including rifampicin, rifapentine and rifabutin, carbamazepine, phenytoin, St. John's wort (*Hypericum perforatum*)) used systemically should be avoided.

CYP3A4 inhibitors

Bedaquiline exposure may be increased during co-administration with inhibitors of CYP3A4.

The short-term co-administration of bedaquiline and ketoconazole (potent CYP3A inhibitor) in healthy subjects increased the exposure (AUC) to bedaquiline by 22% [90% CI (12; 32)]. A more pronounced effect on bedaquiline may be observed during prolonged co-administration of ketoconazole or other inhibitors of CYP3A.

There are no safety data from bedaquiline multiple dose trials which utilised a dose higher than the indicated dose. Due to the potential risk of adverse reactions due to an increase in systemic exposure, prolonged co-administration of bedaquiline and moderate or strong CYP3A4 inhibitors (e.g. ciprofloxacin, erythromycin, fluconazole, clarithromycin, ketoconazole, ritonavir) used systemically for more than 14 consecutive days should be avoided. If co-administration is required, more frequent electrocardiogram monitoring and monitoring of transaminases is recommended (see section "Special warning and precaution for use").

Other antituberculosis medicinal products

The short-term co-administration of bedaquiline with isoniazid/pyrazinamide in healthy subjects did not result in clinically relevant changes in the exposure (AUC) to bedaquiline, isoniazid or pyrazinamide. No dose-adjustment of isoniazid or pyrazinamide is required during co-administration with bedaquiline.

In a placebo-controlled clinical study in patients with multi-drug resistant *Mycobacterium tuberculosis*, no major impact of co-administration of bedaquiline on the pharmacokinetics of ethambutol, kanamycin, pyrazinamide, ofloxacin or cycloserine was observed.

Antiretroviral medicinal products

In an interaction study of single-dose bedaquiline and multiple-dose lopinavir/ritonavir, exposure (AUC) to bedaquiline was increased by 22% [90% CI (11; 34)]. A more pronounced effect on bedaquiline plasma exposures may be observed during prolonged co-administration with lopinavir/ritonavir. This increase is likely due to ritonavir. If the benefit outweighs the risk, SIRTURO may be used with caution when co-administered with lopinavir/ritonavir. Increases in plasma exposure to bedaquiline would be expected when it is co-administered with other ritonavir-boosted HIV protease inhibitors.

Co-administration of single-dose bedaquiline and multiple-dose nevirapine did not result in clinically relevant changes in the exposure to bedaquiline. Clinical data on co-administration of bedaquiline and antiretroviral agents in patients co-infected with human immunodeficiency virus and multi-drug resistant *Mycobacterium tuberculosis* are not available (see section 4.4). Efavirenz is a moderate inducer of CYP3A activity and co-administration with bedaquiline may result in reduced bedaquiline exposure and loss of activity, and is, therefore, not recommended.

QT interval prolonging medicinal products

There is limited information available on the potential for a pharmacodynamic interaction between bedaquiline and medicinal products that prolong the QT interval. In an interaction study of bedaquiline and ketoconazole, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual medicinal products. An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other medicinal products that prolong the QT interval cannot be excluded and frequent monitoring is recommended (see section "Special warning and precaution for use").

QT interval and concomitant clofazimine use

In an open label Phase IIb trial, mean increases in QTcF were larger in the 17 subjects who were using concomitant clofazimine at week 24 (mean change from reference of 31.9 ms) than in subjects who were not using concomitant clofazimine at week 24 (mean change from reference of 12.3 ms) (see section "Special warning and precaution for use").

Paediatric population

Interaction studies have only been performed in adults.

- **Fertility, pregnancy and lactation**

Pregnancy

There are limited data on the use of Bedaquiline in pregnant women. At clinically relevant exposures, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section “Preclinical safety data”).

As a precautionary measure, it is recommended to avoid the use of bedaquiline during pregnancy unless the benefit of therapy is considered to outweigh the risks.

Breastfeeding

It is not known whether bedaquiline or its metabolites are excreted in human milk.

In rats, concentrations of bedaquiline in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma. Body weight decreases in pups were noted in high dose groups during the lactation period (see section “Preclinical safety data”).

Because of the potential for adverse reactions in breastfed infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from bedaquiline therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Fertility

No human data on the effect of bedaquiline on fertility are available. In female rats, there was no effect on mating or fertility with bedaquiline treatment, however some effects were observed in male rats (see section “Preclinical safety data”).

QT interval prolonging medicinal products

There is limited information available on the potential for a pharmacodynamic interaction between bedaquiline and medicinal products that prolong the QT interval. In an interaction study of bedaquiline and ketoconazole, a greater effect on QTc was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual medicinal products. An additive or synergistic effect on QT prolongation of bedaquiline when co-administered with other medicinal products that prolong the QT interval cannot be excluded and frequent monitoring is recommended (see section “Special warning and precaution for use”).

QT interval and concomitant clofazimine use

In an open label Phase IIb trial, mean increases in QTcF were larger in the 17 subjects who were using concomitant clofazimine at week 24 (mean change from reference of 31.9 ms) than in subjects who were not using concomitant clofazimine at week 24 (mean change from reference of 12.3 ms) (see section “Special warning and precaution for use”).

Paediatric population

Interaction studies have only been performed in adults.

- **Fertility, pregnancy and lactation**

Pregnancy

There are limited data on the use of bedaquiline in pregnant women. At clinically relevant exposures, animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section “Preclinical safety data”).

As a precautionary measure, it is recommended to avoid the use of bedaquiline during pregnancy unless the benefit of therapy is considered to outweigh the risks.

Breastfeeding

It is not known whether bedaquiline or its metabolites are excreted in human milk.

In rats, concentrations of bedaquiline in milk were 6- to 12-fold higher than the maximum concentration observed in maternal plasma. Body weight decreases in pups were noted in high dose groups during the lactation period (see section “Preclinical safety data”).

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Because of the potential for adverse reactions in breastfed infants, a decision must be made whether to discontinue breast-feeding or to discontinue/abstain from bedaquiline therapy taking into account the benefit of breast-feeding for the infant and the benefit of therapy for the mother.

Fertility

No human data on the effect of bedaquiline on fertility are available. In female rats, there was no effect on mating or fertility with bedaquiline treatment, however some effects were observed in male rats (see section "Preclinical safety data").

- **Effects on ability to drive and use machines**

Bedaquiline has minor influence on the ability to drive and use machines. Adverse reactions, such as dizziness, may affect the ability to drive or use machines. Patients should be advised not to drive or operate machinery if they experience dizziness while taking bedaquiline.

- **Undesirable effects**

Summary of the safety profile

Adverse drug reactions for bedaquiline were identified from pooled Phase IIb clinical trial data (both controlled and uncontrolled) containing 335 patients who received bedaquiline in combination with a background regimen of tuberculosis medicinal products. The basis of assessment of causality between the adverse drug reactions and bedaquiline was not restricted to these trials, but also on review of the pooled Phase I and Phase IIa safety data. The most frequent adverse drug reactions (> 10.0% of patients) during treatment with bedaquiline in the controlled trials were nausea (35.3% in the bedaquiline group vs 25.7% in the placebo group), arthralgia (29.4% vs 20.0%), headache (23.5% vs 11.4%), vomiting (20.6% vs 22.9%) and dizziness (12.7% vs 11.4%).

Tabulated list of adverse reactions

Adverse drug reactions to bedaquiline reported from controlled trials in 102 patients treated with Bedaquiline are presented in the table below.

Adverse drug reactions are listed by system organ class (SOC) and frequency. Frequency categories are defined as follows: very common ($\geq 1/10$), common ($\geq 1/100$ to $< 1/10$) and uncommon ($\geq 1/1,000$ to $< 1/100$).

System Organ Class (SOC)	Frequency Category	ADRs
Nervous system disorders	Very Common	Headache, dizziness
Cardiac disorders	Common	Electrocardiogram QT prolonged
Gastrointestinal disorders	Very Common	Nausea, vomiting
	Common	Diarrhoea
Hepatobiliary disorders	Common	Transaminases increased*
Musculoskeletal and connective tissue disorders	Very Common	Arthralgia
	Common	Myalgia

* Terms represented by 'transaminases increased' included AST increased, ALT increased, hepatic enzyme increased, hepatic function abnormal, and transaminases increased (see section below).

Description of selected adverse events

Deaths

In the randomised phase IIb study (C208, stage 2) a higher rate of deaths was seen in the Bedaquiline treatment group (12.7%; 10/79 patients) compared to the placebo treatment group (3.7%; 3/81 patients). One death in the Bedaquiline group and one death in the placebo group were reported after the week 120 window. In the Bedaquiline group, all of the five deaths due to tuberculosis occurred in patients whose sputum culture status at last visit was 'not converted'. The causes of death in the remaining Bedaquiline subjects were alcohol poisoning, hepatitis/hepatic cirrhosis, sep-

tic shock/peritonitis, cerebrovascular accident and motor vehicle accident. One of the ten deaths in the Bedaquiline group (due to alcohol poisoning) occurred during the 24-week treatment period. The other nine deaths among those treated with Bedaquiline occurred after completion of treatment with this agent (range 86-911 days post-Bedaquiline; median 344 days). The observed imbalance in deaths between the two treatment groups is unexplained. No discernible pattern between death and sputum culture conversion, relapse, sensitivity to other medicinal products used to treat tuberculosis, human immunodeficiency virus status, or severity of disease could be observed. During the trial, there was no evidence of antecedent significant QT prolongation or clinically significant dysrhythmia in any of the patients that died.

In the Phase IIb, open-label study (C209), 6.9% (16/233) patients died. The most common cause of death as reported by the investigator was tuberculosis (9 patients). All but one patients who died of tuberculosis had not converted or had relapsed. The causes of death in the remaining patients varied.

Description of selected adverse reactions

Cardiovascular

In the controlled Phase IIb study (C208), mean increases from baseline values in QTcF were observed from the first on-treatment assessment onwards (9.9 ms at week 1 for SIRTURO and 3.5 ms for placebo). The largest mean increase from baseline values in QTcF during the 24 weeks of Bedaquiline treatment was 15.7 ms (at week 18). After the end of Bedaquiline treatment (i.e. after week 24), QTcF increases in the Bedaquiline group gradually became less pronounced. The largest mean increase from baseline values in QTcF in the placebo group during the first 24 weeks was 6.2 ms (also at week 18) (see section 4.4).

In the Phase IIb, open label study (C209), where patients with no treatment options received other QT-prolonging medicinal products used to treat tuberculosis, including clofazimine, concurrent use with Bedaquiline resulted in additive QT prolongation, proportional to the number of QT prolonging medicinal products in the treatment regimen.

Patients receiving Bedaquiline alone with no other QT prolonging medicinal product developed a maximal mean QTcF increase over baseline of 23.7 ms with no QT duration in excess of 480 ms, whereas patients with at least 2 other QT prolonging medicinal products developed a maximal mean QTcF prolongation of 30.7 ms over baseline, resulting in a QTcF duration in excess of 500 ms in one patient.

There were no documented cases of Torsade de Pointes in the safety database (see section “Special warnings and precaution for use”). See section 4.5, QT interval and concomitant clofazimine use, for further information regarding patients using clofazimine concomitantly.

Increased transaminases

In study C208 (stage 1 and 2), aminotransferase elevations of at least 3 x ULN developed more frequently in the Bedaquiline treatment group (11/102 [10.8%] versus 6/105 [5.7%]) in the placebo treatment group. In the bedaquiline treatment group, the majority of these increases occurred throughout the 24 weeks of treatment and were reversible. During the investigational phase in Stage 2 of study C208, increased aminotransferases were reported in 7/79 (8.9%) patients in the SIRTURO treatment group compared to 1/81 (1.2%) in the placebo treatment group.

- **Overdose**

Cases of intentional or accidental acute overdose with bedaquiline were not reported during clinical trials. In a study in 44 healthy subjects receiving a single 800 mg dose of bedaquiline, adverse reactions were consistent with those observed in clinical studies at the recommended dose (see section “Undesirable effects”).

There is no experience with the treatment of acute overdose with SIRTURO. General measures to support basic vital functions including monitoring of vital signs and electrocardiogram (QT interval) monitoring should be taken in case of deliberate or accidental overdose. Removal of unabsorbed bedaquiline may be aided by the administration of activated charcoal. Since bedaquiline is

highly protein-bound, dialysis is not likely to significantly remove bedaquiline from plasma. Clinical monitoring should be considered.

Environmental Risk Assessment (ERA)

Environmental risk assessment studies have shown that bedaquiline has the potential to be persistent, bioaccumulative and toxic to the environment (see section “Special precautions for disposal and other handling”).

Pharmaceutical particulars

• **List of excipients**

Lactose monohydrate

Maize starch

Hypromellose

Polysorbate 20

Microcrystalline cellulose

Croscarmellose sodium

Silica, colloidal anhydrous

Magnesium stearate

• **Incompatibilities**

Not applicable.

• **Shelf life**

2 years

• **Special precautions for storage**

This medicinal product does not require any special temperature storage conditions.

Store in the original container or package in order to protect from light.

• **Nature and contents of container**

188 tablets packaged in a white high density polyethylene (HDPE) bottle with child-resistant polypropylene (PP) closure with aluminium induction seal liner.

Carton containing 4 push-through blister strips (containing 6 tablets per strip). Tablets are packaged in aluminium/aluminium foil blisters.

• **Special precautions for disposal and other handling**

This medicinal product may pose a risk to the environment.

Any unused product or waste material should be disposed of in accordance with local requirements (see section “Preclinical safety data”).

4. Legislative regulation

Cohort Event Monitoring of Bedaquiline safety and effectiveness (CEM-BDQ) will be performed in full compliance with:

- Law of the Republic of Belarus of 18.06.1993 No 2435-XII “Public Health Service” with current approved amendments;
- Law of the Republic of Belarus of 20.07.2006 No 161-3 «On medicinal preparations» with current approved amendments;
- Programme No 1-Bdq of 05.05.2015 of Cohort Event Monitoring of BEDAQUILINE safety and effectiveness in combination antituberculosis therapy;
- National Clinical Guidelines for treatment of tuberculosis, Ministry of Health of the Republic of Belarus, 2009.

3. Aims and objectives of the Cohort Event Monitoring of BDQ safety and effectiveness

Aims of the CEM-BDQ:

- 1) Evaluation of the safety and effectiveness profile of Bedaquiline in combination antituberculosis therapy of patients with pre-XDR / XDR-TB.
- 2) Provide health care system with the mechanism of administration of Bedaquiline in combination antituberculosis therapy with positive benefit-risk ratio.
- 3) Implementation of the effective system of continuous safety ATB drugs monitoring and assurance of safety of TB patients.

Objectives of the CEM-BDQ:

- 1) Evaluation of the comparative safety and effectiveness profiles of different combination of Bedaquiline with other antituberculosis drugs.
- 2) Identifying of potential risk factors for adverse drug reactions in pre-XDR / XDR-TB patients administered Bedaquiline in combination antituberculosis therapy.
- 3) Identifying of clinically important drug interaction potentially modifying safety-effectiveness profile of Bedaquiline.
- 4) Evaluation of the safety and effectiveness profiles of Bedaquiline in combination antituberculosis therapy in pre-XDR / XDR-TB patients with different comorbidities.
- 5) Development of risk minimization measures for Bedaquiline in combination antituberculosis therapy in pre-XDR / XDR-TB patients with different risk factors.
- 6) Detecting of ATB ineffectiveness cases, revealing of ineffectiveness reasons, development and implementation of preventive measures.
- 7) Evaluation the rate of non-compliance and of the factors influencing the compliance of Bedaquiline-containing antituberculosis regimen.

4. Methodology of CEM-BDQ

- **Monitored medicine:**

BEDAQUILINE, tablets 100 mg. Trade name SIRTURO[®]. Manufacturer: Kemwell Biopharma Pvt Ltd, India.

- **Monitored patients:**

In monitored cohort will be enrolled 186 adult patients of both sexes with verified diagnosis of pre-XDR / XDR-TB.

- **Design of CEM-BDQ:**

CEM-BDQ will be performed according to the design of open prospective epidemiologic surveillance study.

- **Inclusion – non-inclusion criteria**

Inclusion criteria:

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1. Age more than 18 years.
2. Clinically and laboratory verified diagnosis of pre-XDR / XDR-TB.
3. Impossibility to admit to the standard recommended antituberculosis regimen according to the results of drug susceptibility testing and/or intolerability of ATB drugs.
4. Value of interval QT \leq 440 ms.
5. Level of Aminotransferases activity (ALT, AST) are less than three times the upper limit of normal and total bilirubin is less than 1.5 times the upper limits of normal.
6. Signed patient informed concern.

Non-inclusion criteria:

1. History of hypersensitivity reaction to Bedaquiline.
2. High risk for heart rhythm disorders: QTc interval greater than 500 ms, history of *Torsades de Pointes* or cardiac ventricular arrhythmias, severe coronary artery disease.
3. Pregnancy, breastfeeding period.
4. Refusal to sign patient informed consent.

Exclusion criteria:

1. Decision of patient.
2. Hypersensitivity reactions to bedaquiline.
3. Prolongation of QT interval greater than 500 ms (confirmed by repeat electrocardiogram).
4. Clinically significant ventricular arrhythmia.
7. Increasing of aminotransferases activity (ALT, AST) more than five times the upper limit of normal and total bilirubin more than 2 times the upper limits of normal.
5. Loss to follow-up.

• **Parameters to be monitored in CEM-BDQ**

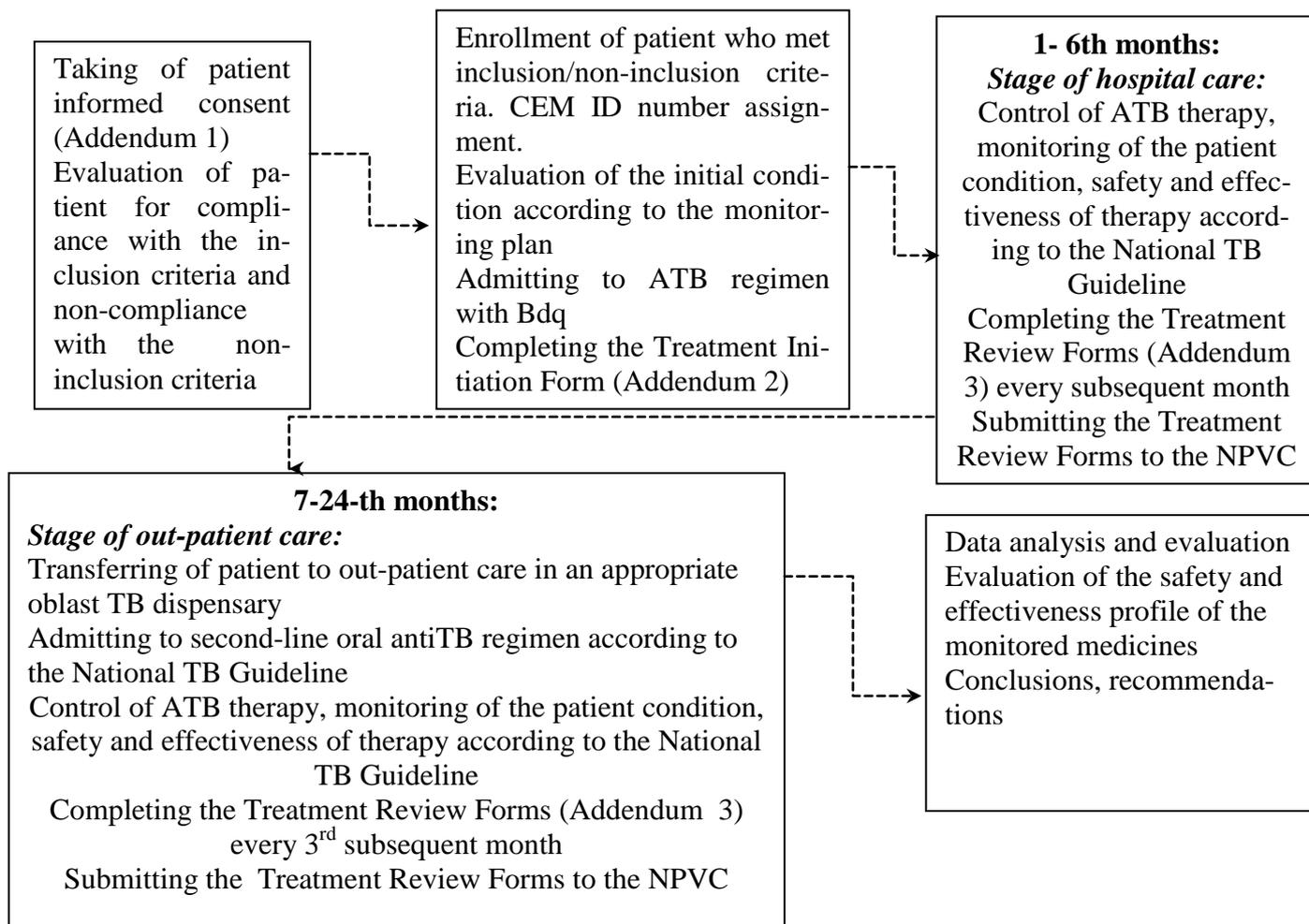
1. Nature, severity and incidence rate of ADRs developed in causal relationship with administration of Bedaquiline.
2. Level of treatment success of combination antituberculosis therapy with Bedaquiline of pre-XDR / XDR-TB patients.
3. Level of refuses of patients to continue antituberculosis therapy with Bedaquiline.

• **Planned duration of participation of patients in CEM-BDQ**

Total duration of participation of every enrolled patient not less than 24 month, including 6 months on Bedaquiline-containing antituberculosis therapy and 18 month on supporting antituberculosis regimen.

• **Plan of enrollment, admitting to the ATB therapy and monitoring patients in CEM-BDQ**

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1. Taking of the informed patient consent – detailed explanation to the patients of all benefits and risks related to Bedaquiline used for therapy of pre-XDR / XDR-TB patients, reasons for inclusion in the cohort event monitoring, requirements to participants. Confirmation by the patient of an awareness of all important information related to participation in CEM-BDQ. Signing of the Informed Consent in case of voluntary consent of patient to be admitted to Bedaquiline-containing antituberculosis regimen and enrolled into the CEM-BDQ. Procedure of the taking of the informed consent is performed according to the appropriate local SOP.
2. Evaluation of patient for compliance with inclusion/non-inclusion criteria – evaluation of the individual clinical and laboratory data of patient for compliance with the inclusion criteria and non-compliance with the non-inclusion criteria of CEM-BDQ.
3. Enrollment of the patient in CEM-BDQ – patients who met inclusion/non-inclusion criteria enrolled into the CEM-BDQ. Every case of the enrollment and compliance with inclusion criteria and non-compliance with non-inclusion criteria is confirmed by the Republican Concilium operated on the basis of the Republican Scientific and Practical Center of Pulmonology and Tuberculosis. In case of non-compliance of the patient to one from inclusion criteria or compliance to the one from non-inclusion criteria and considering the individual ratio of benefit-risk for patient as positive, the Republican Concilium is responsible for the decision for inclusion/non-inclusion of the patient and possible additional risk-minimization measure in case of deviation from the inclusion/non-inclusion terms of the Programme.
4. CEM-BDQ identification number assignment – for fulfillment of data confidentiality requirements all enrolled patient should be assigned with the individual identification number, which includes 3 letters (first letters of family name, patronymic name and first name) and 2 figures (3rd and 4th figure from the year of birth). For instance: Ivanov Victor Petrovich, 1985 year of birth. Individual identification CEM-BDQ number for the patient is IVP85.

5. Evaluation of the initial condition – includes evaluation of the current and past medical condition (comorbidity conditions, adverse symptoms) of patient before admitting to the Bedaquiline therapy, performing of biochemical and specific laboratory testing, instrumental investigations, which are specified by the National TB Guideline and WHO recommendation. Biochemical and laboratory testing include blood and immunologic parameters (WBC, platelets, eosinophils, albumin, ESR, CD4 count), renal function parameters (creatinine, CFR, urea), liver function parameters (ALT, AST, AP, GGTP, bilirubin total), pancreatic function parameters (α – amylase), electrolytes (potassium, calcium, magnesium), carbohydrate metabolism (glucose), purine metabolism (uric acid), thyroid gland function (TSH). Specific laboratory testing is performed (or preliminary performed testing data could be used) for evaluation and verification of pre-XDR / XDR-TB status (sputum smear, sputum culture, drug susceptibility, line probe assay MBT, GeneXpert). Confirmation of non-pregnancy state for the enrolled female (pregnancy test) should be performed directly before enrollment and admitting to the therapy. Special instrumental investigations include evaluation of the cardiac function (ECG) with obligatory estimating of QT value, X-ray examination, estimating of BMI. Other instrumental investigations could be performed when it is required for verification of any comorbid condition.

6. Admitting to the ATB regimen with Bedaquiline – performed by the Republican Concilium according to the WHO recommendations, National TB Guideline and recommendations for administration of Bedaquiline. According to the currently approved recommendation for Bedaquiline the six-month dosing schedule of the medication is as follows:

- **Week 0-2:** Bedaquiline 400 mg (4 tablets of 100 mg) daily (seven days per week)
- **Week 3-24:** Bedaquiline 200 mg (2 tablets of 100 mg) 3 times per week (with at least 48 hours between doses) for a total dose of 600 mg per week.
- **Week 25 (start of month 7) to end of treatment:** Continue other second-line anti-TB drugs only, as per WHO standard recommendations. No bedaquiline is used in this phase of treatment.

The following concomitant antituberculosis regimens for pre-XDR / XDR-TB with Bedaquiline are recommended:

- For patients with XDR-TB:

6BdqLzdCfzTzd(40%Eto/Pto)ImpAmx/ClvZ/8LzdCfzTzd(40%Eto/Pto)MfxZ

- For patients with pre-XDR-TB (with resistance to fluoroquinolones)

6BdqLzdCfzCmTzd(40%Eto/Pto)Z/3LzdCfzTzd(10%PAS)Eto/Pto

- For patients with pre-XDR-TB (with resistance to injectable preparations)

6BdqLzdCfzLfxTzd(40%Eto/Pto)Z/3LzdCfzLfxTzd(40%Eto/Pto)

7. Completing of the Treatment Initiation Form (TIF) (Addendum 2) – performed by the HCPs fulfilled monitoring function and participated in CEM-BDQ. All physical examination data, medical history, clinical, laboratory, instrumental testing data, taken by the patient medicines are included in the Treatment Initiation Form (Addendum 2) and submitted to the National Pharmacovigilance Center.

8. Treatment and monitoring period

- Patients with pre-XDR-TB/XDR-TB, enrolled to the CEM-BDQ, receive administered Bedaquiline with other components of antituberculosis regimen according to the Republican Concilium recommendation. Concomitant therapy is administered when required according to the National TB Guideline recommendations. Regular monitoring of the safety and effectiveness of the patients is performed according to the National TB Guideline recommendations and CEM-BDQ Programme. Safety monitoring of the patients include biochemical and laboratory testing of blood and immunologic parameters (WBC, platelets, eosinophils, albumin, ESR, CD4 count), renal function parameters (creatinine, CFR, urea), liver function parameters (ALT, AST, AP, GGTP, bilirubin total), pancreatic function parameters (α – amylase), electrolytes (potassium, calcium, magnesium), carbohydrate

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metabolism (glucose), purine metabolism (uric acid), thyroid gland function (TSH). Effectiveness of the antituberculosis therapy is evaluated by specific laboratory testing (sputum smear, sputum culture, drug susceptibility MBT) and X-ray examination. Instrumental safety monitoring of the patients include control of ototoxicity (audiogram), ophthalmological toxicity (ophthalmological examination), neurotoxicity (neurological examination), evaluation of the cardiac function (ECG) with obligatory estimating of QT value. Periodicity of biochemical, laboratory, instrumental and specific clinical evaluation is specified by the National TB Guideline recommendations (Table 1). Other laboratory, instrumental or specific clinical investigations could be performed when it is required for verification of adverse events. In case of any deviation in clinical state of the patient or laboratory parameters this event is evaluated and included in Treatment Review Form (Addendum 3).

- Every month from the date of admitting of the patient to Bedaquiline-containing antituberculosis therapy and enrollment in CEM-BDQ the Treatment Review Form is completed (Addendum 3) and submitted to the National Pharmacovigilance Center.

- After completing of 6-months therapy with Bedaquiline the patient is switched to other second-line antituberculosis regimen and transferred for further monitoring to the appropriate TB oblast dispensary according to the residence place.

- Out-patient monitoring is performed by the local HCPs with completing of Treatment Review Form (TRF) every 3 months (Addendum 3) and submitted to the National Pharmacovigilance Center.

- Analysis of the data of Data Collection Forms is performed regularly by the Clinical Review Committee with evaluation and verification of the revealed adverse events, causality assessment, signal detection and realization of risk minimization activity.

- Intermediate evaluation of safety and effectiveness data of monitored medicines is performed every 3 months within CEM.

- Final evaluation of CEM-BDQ data will be performed after completing by 186 enrolled in the CEM-BDQ patients the programme of treatment and monitoring.

Table 1. – Scheme of CEM-BDQ enrollment and monitoring procedures.

Monitored parameters/procedures	0	1	2	3	4	5	6	9	12	15	18	21	24
Evaluation of inclusion/non-inclusion criteria	×												
Evaluation of the initial state, completing of TIF	×												
Administration of ATB regimen with BDQ	×	×	×	×	×	×	×						
Clinical evaluation	×	×	×	×	×	×	×	×	×	×	×	×	×
Biochemical investigation	×	×	×	×	×	×	×	×	×	×	×	×	×
Bacteriological investigation	×	×					×						×
X-ray investigation	×		×		×		×		×		×		×
Audiogram	×		×		×		×		×		×		×
Ophthalmologist evaluation	×			×			×			×			×
Neurological examination	×			×			×			×			×
ECG (with QT)	×	×	×	×	×	×	×	×	×		×		×
Drug susceptibility MBT													×
Safety and effectiveness of ATB evaluation	×	×	×	×	×	×	×	×	×	×	×	×	×
Analysis of safety and effectiveness data	×	×	×	×	×	×	×	×	×	×	×	×	×

5. Procedure of the recording of the monitoring medicine

Standard procedure of the recording of the monitored medicine includes:

- Deed of assignment of the monitored medicines with specifying of the name, bath number, quantity and signed by the responsible person in the clinical site.
- Record of the monitored medicine transferring to clinical sites.

6. Data included in special data collection forms

Two types of the data collection forms will be used in CEM-BDQ for collecting all required data for further safety and effectiveness evaluation. The data required for completing of the forms is submitted in the Addendum 2 and Addendum 3 and include biochemical and laboratory testing of blood and immunologic parameters, renal function parameters, liver function parameters, pancreatic function parameters, electrolytes, carbohydrate metabolism, purine metabolism, thyroid gland function, effectiveness of the antituberculosis therapy parameters, specific parameters for instrumental safety monitoring.

6. Administrative procedures

1. In the case of any deviation or amendment in the CEM-BDQ programme the description of the deviation or planned amendment with specifying of the reason is submitted in the written form within 24 hours:
 - to clinical advisor for adoption;
 - to local ethic committee for adoption;
 - to the National Pharmacovigilance Center.
2. In the case of serious unexpected adverse drug reaction in suspected causal relationship with antituberculosis drugs HCPs responsible for monitoring of the enrolled patient within 3 days should submit ADR reporting form (Addendum 4) in the National Pharmacovigilance Center according to the Resolution of the Ministry of Health No 48 of 17.04.2015.
3. In the case of death in suspected causal relationship with antituberculosis drugs HCPs responsible for monitoring of the enrolled patient within 3 days should submit in the National Pharmacovigilance Center and local ethic committee information about death in form of ADR reporting form with subsequent submitting of autopsy protocol and post-mortem epicrisis.

7. Patients therapy

Combination antituberculosis therapy for the patients admitted to Bedaquiline-containing antituberculosis regimen is performed according to the WHO recommendations and the National TB Guideline. The following concomitant antituberculosis regimens for pre-XDR / XDR-TB with Bedaquiline are recommended:

- For patients with XDR-TB:

6BdqLzdCfzTzd(40%Eto/Pto)ImpAmx/ClvZ/8LzdCfzTzd(40%Eto/Pto)MfxZ

- For patients with pre-XDR-TB (with resistance to fluoroquinolones)

6BdqLzdCfzCmTzd(40%Eto/Pto)Z/3LzdCfzTzd(10%PAS)Eto/Pto

- For patients with pre-XDR-TB (with resistance to injectable preparations)

6BdqLzdCfzLfxTzd(40%Eto/Pto)Z/3LzdCfzLfxTzd(40%Eto/Pto)

After completing of 6-months therapy with Bedaquiline the patient is switched to other second-line antituberculosis regimen according to the recommendations of the National TB Guideline, individual MBT susceptibility data and individual tolerability data. Supporting therapy and therapy for comorbidities are administered according to the National TB Guideline and an appropriate national Clinical Guidelines.

8. Safety and effectiveness monitoring

• Safety and effectiveness monitoring plan

Safety and effectiveness monitoring of the Bedaquiline-containing antituberculosis therapy is performed according to the WHO recommendations and the National TB Guideline. Laboratory and instrumental parameters necessary for monitoring of main types of possible adverse effects and evaluation of effectiveness of antituberculosis therapy is included in the Data Collection Form (Addendum 2 and 3) and involve the following:

Table 2. – Monitoring parameters

Monitoring safety / effectiveness profile component	Monitoring parameters
Hematotoxicity, immunotoxicity	WBC, platelets, eosinophils, albumin, ESR, CD4 count
Hepatotoxicity	ALT, AST, AP, GGTP, bilirubin total
Nephrotoxicity	Creatinine, CFR, urea
Pancreatoxicity	α – amylase
Cardiotoxicity (QT prolongation)	ECG with obligatory estimating of QT value
Electrolyte imbalance	Potassium, calcium, magnesium
Carbohydrate metabolism disturbance	Glucose
Purine metabolism disturbance	Uric acid
Thyreotoxicity	TSH
Neurotoxicity	Neurological examination
Ototoxicity	Audiogram
Ophthalmological toxicity	Ophthalmological examination
Effectiveness of the ATB regimen	Sputum smear, sputum culture, X-ray examination
MTB susceptibility	Drug susceptibility MBT

Other laboratory instrumental investigations could be performed when it is required for verification of any adverse event and comorbid condition.

- **Severity assessment**

For standardized approach for evaluation of the severity of deviations of monitored laboratory parameters will be used the ADR evaluation scale Common Terminology Criteria for Adverse Events (CTCAE), version 4.0 (Addendum 5).

- **Special management recommendation for patient on Bedaquiline therapy**

- **QT interval monitoring and management**

QT prolongation can result in ventricular arrhythmias (Torsades de Pointes) and result in sudden death, and it is imperative that ECGs are used to monitor the QT interval regularly during bedaquiline use. The QT interval must be corrected for the heart rate and the adjustment is referred to as the “QT-corrected (QTc)”. The Fredericia correction method (QTcF) is preferred. QT interval monitoring should preferably be done using ECG machines that directly report the QTc interval. The QT interval must always be corrected for heart rate. A value greater than 440 ms is considered prolonged. A value greater than 480 ms (or an increase of greater than 60 ms from baseline) should trigger electrolyte testing and more frequent ECG monitoring.

A QTcF interval of more than 500 ms is considered dangerous and stopping QT prolonging drugs is indicated.

Low or high serum electrolyte concentrations in the presence of a QT interval prolongation predisposes to arrhythmias. Abnormal electrolytes - most commonly low values due to the injectable agents - should be corrected.

Whenever QTc prolongation is detected (> 480 ms or an increase of > 60 ms from baseline)

- ✓ Repeat ECG to confirm prolongation.
- ✓ Check K^+ , Mg^{++} , and Ca^{++} and correct levels if found to be abnormal and withhold bedaquiline until the electrolytes have normalized;
- ✓ If the QTc interval is between 480 and 500 ms (and the patient is stable and electrolytes within normal values) repeat weekly ECGs to confirm the QTc interval is stable.
- ✓ If the QTc interval of > 500 ms (confirmed by repeat ECG) **discontinue** bedaquiline and all other QT prolonging drugs in the regimen.

Bedaquiline and all other QT prolonging drugs are to be **discontinued** if the patient develops a clinically significant ventricular arrhythmia. If bedaquiline is stopped for QT prolongation, monitor ECGs at least weekly to confirm that the QTcF interval has returned to baseline. If syncope occurs, obtain an ECG to detect QT prolongation.

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Because of the long half-life of bedaquiline, if the ECG has QT prolongation at week 24, ongoing weekly monitoring should take place until the QT interval normalizes (even though the drug is no longer being given).

– Liver function monitoring and management

Because a higher incidence of liver toxicity was seen in the clinical arm of patients on bedaquiline, liver enzymes should be monitored monthly. If aminotransferase elevations are accompanied by total bilirubin elevation $> 2x$ upper limit of normal (ULN), or aminotransferase elevations are $> 5x$ the upper limit of normal, bedaquiline **needs to be discontinued**. Alcohol and other hepatotoxic drugs should be avoided while on bedaquiline, especially in patients with diminished hepatic reserve (eg, chronic hepatitis or cirrhosis).

Monitor symptoms and laboratory tests (ALT, AST, and bilirubin) at baseline, monthly while on treatment, and as needed. An increase of serum aminotransferases to $> 3x$ upper limit of normal should be followed by repeat testing within 48 hours. Testing for viral hepatitis should be performed and other hepatotoxic medications reviewed and be considered for discontinuation.

Evidence of new or worsening liver dysfunction (including clinically significant elevation of aminotransferases and/or bilirubin and/or symptoms such as fatigue, anorexia, nausea, jaundice, dark urine, liver tenderness, hepatomegaly) in patients on bedaquiline should prompt additional evaluation by the prescriber.

Discontinue bedaquiline if:

- ✓ aminotransferase elevations are accompanied by total bilirubin elevation > 2 times upper limit of normal
- ✓ aminotransferase elevations are > 5 times upper limit of normal aminotransferase elevations persist beyond 2 weeks.

9. Data collection and recording

Data collection is performed by physical examination, patient interviewing, biochemical investigation, specific laboratory and microbiological investigation, ECG examination, clinical evaluation by specific profile specialists, audiogram and other required examinations according to the CEM programme and individual clinical state of the patients. Recording of the data is performed in the primary documentation by HCPs responsible for medical care in hospital or out-patient stage and in Data Collection Forms by HCPs responsible for the monitoring patients within CEM-BDQ.

Responsible for the CEM-BDQ Programme development:

Setkina S., Deputy of the Head of the Republican Clinical Pharmacological Laboratory, Center for Examination and Testing in Health Service

Skrahina A., D.M.Sc., Deputy of the Director of the Republican Scientific and Practical Center for Pulmonology and Tuberculosis

Republican Scientific and Practical Center
of Pulmonology and Tuberculosis

Patient ID number _____

INFORMED CONCENT

I, _____,
(family name, first name, patronymic name) _____ (year of birth)
passport No. _____ date of issue “ ____ ” _____

(issued by),
residing at: _____

have carefully read information about cohort event monitoring of safety and effectiveness of bedaquiline, used for treatment of drug-resistant tuberculosis. I have realized the terms of participation in the cohort event monitoring and voluntary consent to receive bedaquiline (SIRTURO, tablets 100 mg, produced by Kemwell Biopharma Pvt Ltd, India) and participate in the cohort event monitoring of safety and effectiveness of bedaquiline in combination antituberculosis therapy of patients with drug-resistant tuberculosis.

I have received detailed explanation of the physician, who is responsible for performing of monitoring _____ about aims and duration of cohort event monitoring, as well as expected effect of the monitored medicine.

I have been informed, that during cohort event monitoring I could experience adverse drug reactions, which could be related to the monitoring medicine.

I have been provided with possibility to ask all interested questions in respect to all aspects of the cohort event monitoring to the physician, responsible for my treatment. I have realized all recommendation, which I have been provided with, as far as I could according to my level of knowledge.

I agreed that the physician responsible for the monitoring in cohort event monitoring contacted my treating physician and informed about my participation in the cohort event monitoring. I have permitted to my treating physician to inform in confidential way the physician responsible for the monitoring about my current clinical state, medical history and harmful habits.

I have agreed to fulfill all instruction within cohort event monitoring, conscientiously cooperate with physician, responsible for my treatment, and immediately inform him about all deteriorations in my condition, changes in my health condition and all unexpected and unusual symptoms, whenever it could arise.

I have been informed, that my name, address and all data about my health condition will be treated confidentially and could be passed only in the Ministry of Health of the Republic of Belarus or in the organization, responsible for performing of the cohort event monitoring.

I have been informed, that I have a right in any moment to terminate my participation in the cohort event monitoring without justification of my decision.

I have been provided with the copy of this Informed Consent. I consent to receive bedaquiline for treating of drug-resistant tuberculosis and participate in the cohort event monitoring of safety and effectiveness of bedaquiline in combination antituberculosis therapy of patients with drug-resistant tuberculosis.

Patient: _____ Sign: _____ Date: _____

I confirm, that I have submitted the detail explanation of the reason, aims and possible risks of this treatment to the patient.

Physician, responsible for monitoring: _____ Sign: _____ Date: _____

I have witnessed the accurate reading of the consent form by the patient, opportunity to ask the questions, detail explanation provided by the physician and voluntary signing of the consent by the patient.

Physician, responsible for treatment: _____ Sign: _____ Date: _____