J-C Health Care Ltd.

Johnson&Johnson

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

מאי 2025

רופא/ה נכבד/ה,
רוקח/ת נכבד/ה,

Sirturo®

סירטורו™

חברת יאנסן ישראל (J-C Health Care Ltd.) מבקשת להודיעכם כי העלון לרופא של התכשיר שבנדון התעדכן במאי 2025.

פרטי העדכון העיקריים מופיעים בהמשך (טקסט שנוסף מסומן באדום, טקסט שהושמט מסומן כטקסט ~~כחול עם קו חוצה~~, טקסט המהווה החמרה מודגש ברקע צהוב) ,אך קיימים עדכונים נוספים.

ההתוויה המאושרת לתכשיר בישראל

SIRTURO is indicated for use as part of an appropriate combination regimen in adult patients with pulmonary tuberculosis (TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

מרכיב פעיל: Bedaquiline (as fumarate) 100mg

העלון המעודכן נשלח לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://israeldrugs.health.gov.il/#!/byDrug.

כמו כן, מצורף לפרסום זה וניתן לקבל העתק מודפס שלהם באמצעות פנייה לבעל הרישום:

ג'יי-סי הלת'קר בע"מ , קיבוץ שפיים, 6099000, טל': 09-9591111.

בברכה,
ויקטוריה גוטליובר-הדדי
רוקחת ממונה
ג'יי-סי הלת' קר בע"מ

J-C Health Care Ltd.

Johnson&Johnson

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

העדכונים העיקריים בעלון לרופא הינם:

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

SIRTURO is indicated for use as part of an appropriate combination regimen in adult patients ~~for~~with pulmonary ~~multidrug-resistant~~ tuberculosis (~~MDR-~~TB) due to *Mycobacterium tuberculosis* resistant to at least rifampicin and isoniazid ~~in adult patients when an effective treatment regimen cannot otherwise be composed for reasons of resistance or tolerability (see sections 4.2, 4.4 and 5.1).~~
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Treatment with SIRTURO should be initiated and monitored by a physician experienced in the management of ~~multi-drug resistant~~ TB due to ~~*Mycobacterium*~~ *M. tuberculosis* resistant to at least rifampicin and isoniazid.
…
The total duration of treatment with SIRTURO is 24 weeks. SIRTURO should be taken with food.
….

Treatment duration
The total duration of treatment with SIRTURO is 24 weeks.
~~Data on longer treatment duration is very limited. In patients with extensive drug resistance, where~~
When treatment with SIRTURO is considered necessary beyond 24 weeks, treatment may be continued up to 40 weeks in adults, at a dose of 200 mg three times per ~~week~~ ~~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 4.8 and 5.1).

Missed doses
…
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. The total dose of SIRTURO during a 7-day period should not exceed the recommended weekly dose (with at least 24 hours between each intake).

Method of administration
…
SIRTURO tablets should be swallowed whole with water and taken with food.

4.4 Special warnings and precautions for use

Resistance to bedaquiline
Bedaquiline ~~must~~ should only be used in an appropriate combination regimen for ~~MDR-TB~~ treatment of pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid as recommended by official guidelines, such as from the WHO, to prevent development of resistance to bedaquiline (see section 4.2).
~~Mortality~~
~~In the 120-week C208 trial where SIRTURO 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 5.1). The imbalance in deaths is unexplained; no evidence has been found for a causal relationship with SIRTURO treatment. For additional information on deaths in the C209 trial, see section 5.1.~~

J-C Health Care Ltd.

Johnson&Johnson

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

QT prolongation ~~Cardiovascular safety~~
SIRTURO ~~Bedaquiline~~ may prolongs the QTc interval. An electrocardiogram should be obtained before initiation of treatment with SIRTURO and at least monthly after starting treatment to monitor the QTc interval~~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 4.5 and 4.8).

When bedaquiline is co-administered with other medicinal products that prolong the QTc interval (including clofazimine, delamanid or fluoroquinolones~~and levofloxacin~~), an additive ~~or synergistic~~ effect on QT prolongation is expected~~cannot be excluded~~ (see section 4.5). Treatment with SIRTURO may be considered after a favourable benefit-risk assessment and with ECG monitoring. ~~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 4.5).~~

Hepatic safety

Increases in transaminases ~~or aminotransferase elevations~~ accompanied by total bilirubin ≥ 2x ULN were seen in clinical trials during administration of SIRTURO with the background regimen (see section 4.8). ….

CYP3A4 inducers
Bedaquiline is metabolised by CYP3A4. Co-administration of ~~bedaquiline~~ SIRTURO with moderate or strong ~~and medicinal products that induce~~ CYP3A4 inducers~~may~~ decreases bedaquiline plasma concentrations and may reduce the~~its~~ therapeutic effect of SIRTURO. Co-administration of ~~bedaquiline~~ SIRTURO and moderate or strong CYP3A4 inducers used systemically, such as efavirenz and rifamycins (i.e., rifampicin, rifapentine and rifabutin) should, therefore, be avoided (see section 4.5).

~~*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 x 106 cells/l (N = 22; see section 4.5).~~

…

J-C Health Care Ltd.

Johnson&Johnson

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

4.5 Interaction with other medicinal products and other forms of interaction

…

CYP3A4 inducers

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

…..

In the Phase III study, co-administration of the weak CYP3A4 inducer nevirapine and SIRTURO as part of combination therapy for up to 40 weeks in patients co-infected with HIV resulted in a mild decrease in average bedaquiline exposure (AUC) compared to a subgroup without HIV co-infection. This exposure difference was however not associated with a reduction in therapeutic effect. Therefore, no dose adjustment is needed when co-administering SIRTURO with weak CYP3A4 inducers.

CYP3A4 inhibitors

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

~~The short-term co-administration of bedaquiline and ketoconazole (potent CYP3A4 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 CYP3A4.~~

~~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 4.4).~~

Co-administration of SIRTURO and CYP3A4 inhibitors does not have a clinically relevant effect on bedaquiline exposure. Therefore, the co-administration of SIRTURO and CYP3A4 inhibitors is allowed, and no dose adjustment is needed.

The short-term co-administration of bedaquiline and ketoconazole (strong CYP3A4 inhibitor) in healthy adults increased the mean bedaquiline exposure (AUC) by 22% [90% CI (12; 32)]. In healthy adults, 10 days of co-administration of another strong CYP3A4 inhibitor, clarithromycin, with single-dose bedaquiline increased the mean bedaquiline exposure (AUC) by 14% [90% CI (9; 19)]. A more pronounced effect on bedaquiline may be observed during prolonged co-administration of CYP3A4 inhibitors.

In the Phase III trial, long-term co-administration of SIRTURO as part of a combination therapy and lopinavir/ritonavir in patients co-infected with HIV resulted in a mild increase in mean bedaquiline exposure at Week 24 compared to a subgroup without HIV co-infection. No dose adjustment is required.
In the open-label Phase IIb trial, long-term co-administration of clofazimine and SIRTURO, as part of a combination therapy for up to 24 weeks, did not affect bedaquiline exposure.

Other antituberculosis medicinal products

…

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

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

~~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. Published data on patients treated with bedaquiline as part of therapy for drugresistant TB and lopinavir/ritonavir-based ART have shown that bedaquiline exposure (AUC) over 48 hours was increased approximately 2-fold. 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 coadministered with other ritonavir-boosted HIV protease inhibitors. Of note, no change in bedaquiline dosing is recommended in case of co-treatment with lopinavir/ritonavir or other ritonavir-boosted HIV protease inhibitors. There are no data to support a lowered bedaquiline dose in such circumstances.~~

~~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 CYP3A4 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 4.4).~~

~~QT interval and concomitant clofazimine use~~

In an open label Phase IIb trial in adults, ~~mean~~additive increases in QTcF were observed~~larger~~ in the 17 patients~~subjects~~ who were using concomitant clofazimine at W~~w~~eek 24 (mean change from reference QTcF~~of~~ 31.9 ms compared to 12.3 ms~~) than~~ in patients~~subjects~~ who were not using concomitant clofazimine) ~~at week 24 (mean change from reference of 12.3 ms) (see section 4.4).~~

In the Phase III trial, additive increases in QTcF were observed when combining clofazimine and levofloxacin with SIRTURO (see sections 4.4 and 4.8).

In an interaction study of bedaquiline and ketoconazole in healthy adults, a greater effect on QTcF was observed after repeated dosing with bedaquiline and ketoconazole in combination than after repeated dosing with the individual drugs (see sections 4.4 and 4.8).

4.8 Undesirable effects

Summary of the safety profile

Adverse ~~drug~~ reactions for SIRTURO were identified from ~~pooled~~ Phase IIb clinical trial data (both

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

controlled and uncontrolled C208 and C209) ~~containing~~ in 335 adult patients who received SIRTURO for 8 weeks or 24 weeks~~in combination with a background regimen of tuberculosis medicinal products.~~ No new adverse reactions were identified in the Phase III active-controlled trial including 354 patients who received SIRTURO for 40 weeks or 28 weeks. In these studies, patients received SIRTURO in combination with other antimycobacterial drugs~~The basis of assessment of causality between the adverse drug reactions and SIRTURO 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) reported during treatment with SIRTURO in the open-label Phase III ~~controlled~~ trial~~s~~ were QT prolongation (61% in the SIRTURO group vs 56% in the control group), nausea (54% vs 63%), vomiting (54% vs 62%), arthralgia (45% vs 33%), transaminases increased (30% vs 29%), dizziness (18% vs 21%) and headache (17% vs 18%)~~nausea (35.3% in the SIRTURO 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

…

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

[a] Frequencies derived from Phase III trial STREAM Stage 2 40-week, all-oral treatment of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase).

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

[c] Incidence of transaminases increased in the controlled Phase IIb study was Common (6.9% in the SIRTURO group and 1% in placebo control).

[d] Incidence of QT prolonged in Phase IIb study was Common (2.9% in the SIRTURO group and 3.8% in placebo control).

Description of selected adverse reactions

QT prolongation

Clinical trials of SIRTURO in adult TB patients collectively show a mild (<10 ms) QTcF increase throughout treatment attributable to M2, the major bedaquiline metabolite. In combination with other QT-prolonging drugs (e.g., clofazimine, delamanid, or fluoroquinolones), a prolongation of the QTc interval not more than additive was observed (see section 4.5).

~~*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~~ Week 1 for SIRTURO and 3.5 ms for placebo). The largest mean increase (at Week 18)~~from baseline values~~ in QTcF during the 24 weeks of ~~SIRTURO~~ treatment with SIRTURO was 15.7 ms , compared to 6.2 ms in the placebo group~~(at~~

~~week 18)~~. After ~~the end of SIRTURO~~ treatment with SIRTURO ended~~(i.e. after week 24)~~, the QTcF gradually decreased, and the mean value was similar to that in the placebo group by study Week 60 ~~increases in the SIRTURO 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~~pulmonary TB, including clofazimine, concurrent use with SIRTURO resulted in additive QT prolongation, proportional to the number of QT ~~prolonging medicinal products in the treatment regimen~~. In patients taking SIRTURO with no other QT-prolonging drugs, there were no patients with QTcF interval durations above 480 ms, and in patients who were taking at least two other QT-prolonging drugs, there was one patient with a QTcF interval duration above 500 ms.

~~Patients receiving SIRTURO 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 4.4). See section 4.5, QT interval and concomitant clofazimine use, for further information regarding patients using clofazimine concomitantly.~~

In the controlled Phase III study, in which the 40-week SIRTURO and active control treatment groups included both clofazimine and a fluoroquinolone, the mean QTcF gradually increased from baseline over the first 10 to 14 weeks, when a plateau was reached and additive QT prolongation was observed. The highest mean QTcF increase from baseline was 34.5 ms for the SIRTURO-containing group and 29.9 ms for the non-SIRTURO-containing control. Throughout treatment, mean QTcF increase was less than 10 ms higher in the SIRTURO-containing group compared to the control. Upon treatment completion mean QTcF decreased steadily. QTcF values ≥500 ms were observed in 5.2% of patients in the SIRTURO-containing group compared to 7.4% in the non-SIRTURO-containing control group (see sections 4.4 and 4.5).

Increased transaminases
In ~~study~~ Study C208 (S~~s~~tage 1 and 2), transaminase ~~aminotransferase~~ elevations of at least 3 x ULN developed more frequently in the SIRTURO treatment group (11/~~102~~ 101[10.~~8~~9%] versus 6/~~105~~ 104 [5.~~7~~8%]) in the placebo treatment group. In the SIRTURO treatment group, the majority of these increases occurred throughout the 24 weeks of treatment and were reversible. During the investigational phase in ~~stage~~ Stage 2 of ~~study~~ Study C208, increased transaminases ~~aminotransferases~~ were reported in 7/~~79~~ 78 (~~8~~9.~~9~~0%) patients in the SIRTURO treatment group compared to 1/~~81~~ 80 (1.~~2~~3%) in the placebo treatment group.

In the STREAM Stage 2 study, increased transaminases were reported in 63/211 (29.9%) patients in the 40-week SIRTURO treatment group versus 59/202 (29.2%) patients in the 40-week active control group.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

...

Pharmacodynamic effects

Bedaquiline has activity against ~~*Mycobacterium*~~ *M. tuberculosis* complex strains with a minimal

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

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 of ≤ 0.008 to ~~-0.2512~~ mg/~~L1~~. …..
…Bedaquiline is bacteriostatic for many non-tuberculous mycobacterial species. *Mycobacterium xenopi*, *Mycobacterium novocastrense*, *Mycobacterium shimoidei, Mycobacterium flavescens* and non-mycobacterial species are considered inherently resistant to bedaquiline.
…

Susceptibility testing breakpoints
MIC (minimum inhibitory concentration) interpretive criteria for susceptibility testing have been established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) for bedaquiline and are listed here: https://www.ema.europa.eu/documents/other/minimum-inhibitoryconcentration-mic-breakpoints_en.xlsx
~~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~~
~~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~~
…
Inherently resistant organisms
Mycobacterium xenopi
Mycobacterium novocastrense
Mycobacterium shimoidei
Mycobacterium flavescens
Non-mycobacterial species

Clinical efficacy and safety

~~The following definitions apply for resistance categories used:~~
~~Multi-drug resistant *Mycobacterium tuberculosis* (MDRH&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 adult patients with sputum smear-positive pulmonary ~~MDRH&R- and pre-XDR-~~TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid, including patients with resistance to second-line injectables or fluoroquinolones. ….

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

A final evaluation was conducted at Week 120. Main demographics for the ITT population 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 in the mITT population with full characterisation of resistance status, 76% (~~84~~85/~~111~~112) were infected with an ~~MDRH&R-TB~~ *M. tuberculosis* strain resistant to rifampicin and isoniazid and 24% (27/~~111~~112) with a ~~pre-XDR-TB~~ *M. tuberculosis* strain also resistant to second-line injectables or fluoroquinolones.

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~~ MGIT 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 a *M. tuberculosis* strain resistant to rifampicin and isoniazid ~~pre-XDR-TB~~ and patients with a *M. tuberculosis* strain also resistant to second-line injectables or fluoroquinolones ~~MDRH&R-TB~~.

Table 1: Culture Cconversion Status in C208
Patients with a *M. tuberculosis* strain resistant to rifampicin and isoniazid ~~MDRH&R-TB~~
Patients ~~infected~~ with a *M. tuberculosis* strain resistant to rifampicin and isoniazid, and also to second-line injectables or fluoroquinolones pre-XDR-TB

During the trial, 12.7% (10/79) of the patients died in the SIRTURO treatment group (N=79) compared to 3.7% (3/81) of the patients in the placebo group (N=81). One death occurred during administration of SIRTURO. The median time to death for the remaining nine patients was 344 days after last intake of SIRTURO. In the SIRTURO treatment group, the most common cause of death as reported by the investigator was TB (5 patients). The causes of death in the remaining patients treated with SIRTURO varied. During the trial, there was no evidence of antecedent significant QTcF prolongation or clinically significant dysrhythmia in any of the patients who died.

Study C209 evaluated the safety, tolerability, and efficacy of 24 weeks treatment with open-label SIRTURO as part of an ~~individualized~~ individualised treatment regimen in 233 adult patients who were sputum smear positive within 6 months prior to screening. This study included patients with *M. tuberculosis* strains of all three resistance categories (resistant to rifampicin and isoniazid, also resistant to second-line injectables or fluoroquinolones, and also resistant to second-line injectables and fluoroquinolones ~~MDRH&R-, pre-XDR- and XDR-TB~~).

…

Conversion rates at Wweek 24 were highest (87.1%; 81/93) in patients with *M. tuberculosis* isolates resistant to only rifampicin and isoniazid ~~MDRH&R-TB~~, 77.3% (34/44) in ~~pre-XDR-TB~~ patients with pulmonary TB due to *M. tuberculosis* resistant to rifampicin, isoniazid, second-line injectables or fluoroquinolones, and lowest (54.1%; 20/37) in ~~XDR-TB~~ patients with *M. tuberculosis* isolates resistant to rifampicin, isoniazid, second-line injectables and fluoroquinolones. Extent of resistance based on central laboratory drug susceptibility testing results was not available for ~~32~~ 31 ~~subjects~~ patients in the mITT population. These patients ~~subjects~~ were excluded from the subgroup analysis by extent of resistance of ~~*Mycobacterium*~~ *M. tuberculosis* strain.

At ~~week~~ Week 120, sputum culture conversion was seen in 148/205 (72.2%) patients. Conversion rates at W~~w~~eek 120 were highest (73.1%; 68/93) in patients with *M. tuberculosis* isolates resistant to only rifampicin and isoniazid ~~MDRH&R-TB~~, 70.5% (31/44) in ~~pre-XDR-TB~~ patients with pulmonary

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

TB due to *M. tuberculosis* resistant to rifampicin, isoniazid, second-line injectables or fluoroquinolones and lowest (62.2%; 23/37) in ~~XDR-TB~~ patients with *M. tuberculosis* isolates resistant to rifampicin, isoniazid, second-line injectables and fluoroquinolones.

…

~~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.~~
In the open-label C209 trial, 6.9% (16/233) of the patients died. The most common cause of death as reported by the investigator was TB (9 patients). Eight of nine patients who died of TB had not converted or had relapsed. The causes of death in the remaining patients varied.

STREAM Stage 2 was a Phase III, open-label, multicentre, active-controlled, randomised trial conducted to evaluate the efficacy and safety of SIRTURO co-administered with other oral anti-TB drugs for 40 weeks in patients with sputum smear-positive pulmonary TB caused by *M. tuberculosis* that was resistant to at least rifampicin, with or without resistance additionally to isoniazid and/or second-line injectable agents or fluoroquinolones (but not both).

Patients were randomised to one of four treatment groups:
- Group A (N=32), the locally used treatment in accordance with 2011 WHO treatment guidelines with a recommended 20-month duration
- Group B (N=202), a 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high-dose isoniazid, and prothionamide in the first 16 weeks (intensive phase)
- Group C (N=211), a 40-week, all-oral treatment of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase)
- Group D (N=143), a 28-week treatment consisting of SIRTURO, levofloxacin, clofazimine, and pyrazinamide supplemented by kanamycin injectable and a higher isoniazid dose for the first 8 weeks (intensive phase)

SIRTURO was administered as 400 mg once daily for the first 2 weeks and 200 mg 3 times/week for the following 38 weeks (in Group C) or 26 weeks (in Group D). Changes in treatment regimen were permitted at the discretion of the investigator in all groups. Enrolment in Groups A and D was stopped prematurely due to changes in the standard of care for TB treatment.

The primary objective was to assess whether the proportion of patients with a favourable efficacy outcome in Group C was noninferior to that in Group B at Week 76.

The primary efficacy outcome measure was the proportion of patients with a favourable outcome at Week 76. A favourable outcome at Week 76 was defined as last 2 consecutive cultures negative and no unfavourable outcome. An unfavourable outcome at Week 76 encompassed clinically relevant changes in treatment, all cause mortality, at least 1 of the last 2 culture results positive, or no culture results within the Week 76 window.

In the overall study population (N=588), 59.9% were male, median age was 32.7 years, 47.3% were Asian, 36.6% were Black, 16.2% were White and 16.5% were HIV-coinfected. Most patients had cavitation (73.1%), with multiple cavities in 55.3% of patients. Of the 543 patients in the primary efficacy population (mITT

population, defined as patients with a positive culture for *M. tuberculosis* at screening or randomisation), 12.5% of the patient's *M. tuberculosis* isolates were resistant to rifampicin while susceptible to isoniazid, 76.4% had resistance to at least rifampicin and isoniazid, and 11% had resistance to rifampicin, isoniazid and either second-line injectables or fluoroquinolones.

Table 2 shows the proportion of patients with a favourable or unfavourable outcome at Week 76 in the STREAM Stage 2 Phase III trial. The proportion of participants with a favourable outcome at Week 76 was 82.7% in Group C compared to 71.1% in Group B. The main reason for an unfavourable outcome in both groups was extension or modification of the assigned treatment regimen. Limitations of the study included its open-label design; changes to the allocated treatment regimens were permitted in case of treatment failure, recurrence or serious toxicity.

Table 2: Primary Analysis in STREAM Stage 2 (Phase III Trial)

	mITT Population	
	SIRTURO[a] (N=196)	**Active Control[b] (N=187)**
Favourable outcome at Week 76 n (%)	162 (82.7)	133 (71.1)
Unfavourable outcome at Week 76 n (%)	34 (17.3)	54 (28.9)
Reasons for unfavourable outcome through Week 76[c]		
Treatment modified or extended	16 (8.2)	43 (23.0)
No culture results within Week 76 window	12 (6.1%)	7 (3.7)
Death through Week 76	5 (2.6)	2 (1.1)
At least one of last 2 cultures positive at Week 76	1 (0.5)	2 (1.1)

mITT = modified intent-to-treat

[a] Group C 40-week, all-oral regimen of SIRTURO, levofloxacin, clofazimine, ethambutol, and pyrazinamide, supplemented by high-dose isoniazid and prothionamide in the first 16 weeks (intensive phase).

[b] Group B 40-week control treatment of moxifloxacin or levofloxacin, clofazimine, ethambutol, pyrazinamide, supplemented by injectable kanamycin, high dose isoniazid and prothionamide in the first 16 weeks (intensive phase).

[c] Patients were classified by the first event that made the patient unfavourable. Of the patients with an unfavourable outcome at Week 76 in the control group, 29 patients had a treatment modification from their allocated treatment that included SIRTURO as part of a salvage regimen.

The frequency of deaths was similar across treatment groups through Week 132. In the 40-week SIRTURO group, 11/211 (5.2%) patients died; the most common cause of death was related to TB (5 patients). In the 40-week active control group, 8/202 (4.0%) patients died, including 4 of 29 patients who received SIRTURO as part of a salvage treatment; the most common cause of death was related to respiratory pathology. The adjusted difference in proportion of fatal adverse events between the 40-week SIRTURO group and the 40-week active control group was 1.2% [95% CI (-2.8%; 5.2%)].

~~Mortality~~

~~In the randomised Phase IIb study (C208, stage 2) a higher rate of deaths was seen in the SIRTURO treatment group (12.7%; 10/79 patients) compared to the placebo treatment group (3.7%; 3/81 patients). One death in the SIRTURO group and one death in the placebo group were reported after the week 120 window. In the SIRTURO 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 SIRTURO patients were alcohol poisoning, hepatitis/hepatic cirrhosis, septic shock/peritonitis, cerebrovascular accident and motor vehicle accident. One of the ten deaths in the SIRTURO group (due to alcohol poisoning) occurred during the 24 week treatment period. The other nine deaths among those treated with SIRTURO occurred after completion of treatment with this agent (range 86-911 days post SIRTURO; 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~~

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

~~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.~~
....

5.2 Pharmacokinetic properties

The pharmacokinetic properties of bedaquiline have been evaluated in ~~adult~~ healthy adults ~~subjects~~ and in adult ~~multi-drug resistant tuberculosis-infected~~ patients with active TB. Exposure to bedaquiline was lower in ~~multi-drug resistant tuberculosis-infected~~ patients with pulmonary TB due to *M. tuberculosis* resistant to at least rifampicin and isoniazid than in healthy ~~subjects~~adults.

In adult patients with pulmonary TB, following 2 weeks of 400 mg bedaquiline once daily, mean (SD) Cmax and AUC24h, ng·h/mL were 3060 (1124) ng/mL and 41510 (15064) ng·h/mL, respectively, for bedaquiline and 326 (135) ng/mL and 7267 (3029) ng·h/mL, respectively, for the M2 metabolite. Following 38 weeks of 200 mg bedaquiline three times weekly, mean (SD) Cmax and AUC168h, ng·h/mL were 1787 (666) ng/mL and 168376 (74476) ng·h/mL, respectively, for bedaquiline and 246 (103) ng/mL and 39540 (17220) ng·h/mL, respectively, for the M2 metabolite.

Absorption
Maximum plasma concentrations (Cmax) are typically achieved at about 5 hours post-dose. Cmax 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 for 14 days ~~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.

Special populations
…
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.
In five patients 65 to 69 years of age, the systemic bedaquiline exposure was similar to that of other adults.

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 lower bedaquiline exposure in Black patients was not associated with lower efficacy in clinical trials, and no dose adjustment is needed.~~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.~~

5.3 Preclinical safety data
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.

J-C Health Care Ltd.

Johnson&Johnson

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

Compared to the exposures (AUC) observed in ~~subjects~~ patients with pulmonary ~~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.

העדכונים העיקריים בעלון לצרכן הינם:

1. למה מיועדת התרופה?

סירטורו מיועדת לטיפול בשחפת ריאות במבוגרים שנגרמת על ידי חיידק mycobacterium tuberculosis ועמידה לטיפול של לפחות ריפמפיצין ואיזוניאזיד ~~עמידה לתרופות במבוגרים~~, כחלק מטיפול משולב עם תרופות נוספות, ~~כאשר אין משטר טיפולי יעיל אחר, עקב עמידות או אי סבילות~~.

2. לפני השימוש בתרופה:

אזהרות מיוחדות הנוגעות לשימוש בתרופה
לפני הטיפול בסירטורו ספר לרופא אם:

- ...
- אתה לוקח תרופות אחרות, כי חלקן עלולות להגביר סיכון לתופעות לוואי
- ..
- יש לך רמות אשלגן נמוכות בדם. זאת ניתן לראות בבדיקות דם.

אינטראקציות/תגובות בין תרופתיות
אם אתה לוקח או אם לקחת לאחרונה תרופות אחרות, כולל תרופות ללא מרשם ותוספי תזונה, ספר על כך לרופא או לרוקח.

התרופות הבאות הן דוגמאות לתרופות אותן עשויים ליטול מטופלים עם שחפת ריאות הנגרמת על ידי mycobacterium tuberculosis העמידה לטיפול של לפחות ריפמפיצין ואיזוניאזיד ~~עמידה לטיפול תרופתי~~, ועלולות לגרום לאינטראקציות עם סירטורו:

שם התרופה (חומר פעיל)	מטרת השימוש
ריפאמפיצין, ריפאפנטין, ריפאבוטין	לטיפול בזיהומים מסוימים כגון שחפת (~~תרופות אנטימיקובקטריאליות~~ אנטימיקובקטריאלים)
~~קטוקונאזול, פלוקונאזול~~	~~לטיפול בזיהומים פטרייתיים (אנטיפונגלים)~~
אפאבירנז, אטראבירין, ~~לופינאביר/ריטונאביר~~	לטיפול בזיהום HIV (אנטירטרווירלי מעכבי נונ-נוקלאוטיד רברס טרנסקריפטז, ~~אנטירטרווירלי מעכבי פרוטאזות~~)
~~קלריתרומיצין~~	~~לטיפול בזיהומים מסוימים כגון צרעת (תרופה אנטי מיקובקטריאלית)~~
קארבאמאזפין, פניטואין	לטיפול בהתקפים אפילפטיים (נוגדי פרכוס)
סנט ג'ונס וורט (היפריקום פרפורטום)	תכשיר צמחי להקלת חרדה
~~ציפרופלוקסצין, אריתרומיצין~~	~~לטיפול בזיהומים בקטריאלים (אנטיבקטריאלים)~~

J-C Health Care Ltd.

Johnson&Johnson

Kibbutz Shefayim 6099000, ISRAEL
tel +972-9-959-1111
fax +972-9-958-3636

3. כיצד תשתמש בתרופה?

נטילת סירטורו:

- תמיד יש ליטול סירטורו עם מזון. המזון יסייע להשגת הרמות הנכונות של התרופה בגוף.

4. תופעות לוואי

תופעות לוואי שכיחות מאוד (מופיעות ביותר ממשתמש אחד מעשרה)

- אק"ג (רישום הפעילות החשמלית של הלב) לא תקין שנקרא "הארכת מקטע QT ". ספר מייד לרופא אם התעלפת.
- עליה באנזימי כבד (ניתן לראות בבדיקות דם)

....

תופעות לוואי שכיחות (מופיעות ב- 1-10 משתמשים מתוך 100)

- ~~אק"ג (רישום הפעילות החשמלית של הלב) לא תקין שנקרא "הארכת מקטע QT ". ספר מייד לרופא אם התעלפת.~~
- ~~עליה באנזימי כבד (ניתן לראות בבדיקות דם)~~

...