EU Risk Management Plan for SIILTIBCY, solution for injection

RMP version to be assessed as part of this application:

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Rationale for submitting an updated RMP: RMP updated according to European Medicines Agency (EMA) CHMP 2nd List of Outstanding Issues (LoOI, Procedure No. EMA/H/C/6177) dated 27-June-2024

Summary of significant changes in this RMP: Wording on the therapeutic indications of the product was modified in Part I: Product overview and in the Summary of risk management plan for SIILTIBCY (rdESAT-6 and rCFP-10) section I. The medicine and what it is used for. The wording was now modified by removing the diagnostic evaluations that could be used in combination with SIILTIBCY and adding that the product is for diagnostic aid for detection.

QPPV name: Dr. Marcus May

QPPV oversight declaration: The content of this RMP has been reviewed and approved by the marketing authorisation applicant's QPPV. The signature is available on file.

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Table of abbreviations

AIDS	Acquired immune deficiency syndrome
ART	Antiretroviral therapy
ATC	Anatomical therapeutic chemical
BCG	Bacille Calmette-Guérin
CFP-10	10 kD culture filtrate protein
CNS	Central nervous system
COVID-19	Coronavirus disease
Cy-Tb	Mixture of rdESAT-6 + rCFP-10
DK	Denmark
DTH	Delayed-type hypersensitivity
ECDC	European Centre for Disease Prevention and Control
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
EPAR	European public assessment report
ESAT-6	6 kD early secretory antigenic target
EU	European Union
F	Female
GLP	Good laboratory practice
HED	Human equivalent dose
HIV	Human immunodeficiency virus
ICH	International Council for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use
i.d.	Intradermal
IGRA	Interferon gamma release assay
INF-γ	Interferon gamma
INN	International non-proprietary name
i.v.	Intravenous
LoQ	List of questions
M	Male
MA	Marketing authorisation
MAA	Marketing authorisation application
MAH	Marketing authorisation holder
Mtb	*Mycobacterium tuberculosis*
N	Number
PCR	Polymerase chain reaction
PL	Patient information leaflet
PSUR	Periodic safety update report

PPD	Purified protein derivative
PPD RT 23	Purified protein derivative rinsed tuberculin (batch) 23, Statens Serum Institut, 2 T.U./0.1 mL
QFT	QuantiFERON®-TB Gold In-Tube. In-vitro diagnostic test for the diagnosis of tuberculosis infection
rdESAT-6	Recombinant dimer of ESAT-6
rCFP-10	Recombinant CFP-10
RMP	Risk management plan
s.c.	Subcutaneous
SII	Serum Institute of India Pvt. Ltd.
SIILTIBCY	Mixture of rdESAT-6 + rCFP-10
SmPC	Summary of Product Characteristics
SSI	Statens Serum Institut
TB	Tuberculosis
TST	Tuberculin skin test
TU	Tuberculin units
UK	United Kingdom
USA	United States of America
WHO	World Health Organization

Part I: Product(s) Overview

Table Part I.1 – Product(s) Overview

Active substance(s) **(INN or common name)**	Recombinant dimer of *Mycobacterium tuberculosis* (Mtb) 6 kDa early secretory antigenic target (rdESAT-6) and recombinant 10 kDa culture filtrate protein of Mtb (rCFP-10)
Pharmacotherapeutic group(s) (ATC Code)	Therapeutic category: Tuberculosis diagnostics ATC code: not yet assigned
Marketing Authorisation Applicant	Serum Life Science Europe GmbH Ahrensburger Str. 1 30659 Hannover Germany
Medicinal products to which this RMP refers	1
Invented name(s) in the European Economic Area (EEA)	SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class: Immunological recombinant antigens
	Summary of mode of action: In case of infection with Mtb, SIILTIBCY induces a delayed-type hypersensitivity reaction directed by cytokines, which are released by TH1 cells after stimulation by the specific antigens included in SIILTIBCY. This reaction is seen as an induration at the site of injection. The induration reaches its maximum 48–72 hours after administration.
	Important information about its composition: One dose contains: rdESAT-6: 0.05 µg rCFP-10: 0.05 µg Recombinant dimer of rdESAT-6 and rCFP-10 derived from Mtb and cloned and expressed on *Lactococcus lactis* cells.
Hyperlink to the Product Information	The production information including the SmPC and the PL is included within Module 1.3.1 of the eCTD sequence.

Indication(s) in the EEA	Current: SIILTIBCY is indicated as a diagnostic aid for detection of *Mycobacterium tuberculosis* infection, including disease, in adults and children aged 28 days or older. This medicinal product is for diagnostic use only.
	Proposed: Not applicable
Dosage in the EEA	Current: 0.1 mL administered via intradermal injection using the Mantoux technique.
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Solution for injection. Clear, colourless to pale-yellow solution, with a pH of 7.2-7.6. (0.5 microgram + 0.5 microgram)/mL solution for injection
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	Yes

Part II: Safety specification

Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Diagnosis of infection with *Mycobacterium tuberculosis* (Mtb) in adults and paediatric individuals older than 28 days

Incidence: According to the World Health Organization (WHO), 10.6 million (9.9-11 million) new (incident) tuberculosis (TB) cases were estimated, and 1.6 million people died from the disease in 2021, including 0.21 million among people with human immunodeficiency virus (HIV) infection (WHO, 2022). The incidence rate rose by 3.6% between 2020 and 2021, reversing declines of about 2% per year for most of the previous 2 decades. This reflects the impact of disruptions to essential TB services during the Coronavirus disease (COVID-19) pandemic (WHO, 2022). In 2020, 33,148 cases of TB were reported in 29 European Union and European Economic Area (EU/EEA) countries (ECDC, 2022a). In 2019, a number of 55,000 cases was estimated in the EU/EEA, as well as 247,000 cases in the total European region (ECDC, 2021). Although the number of TB deaths fell by 5.9% between 2015 and 2021, TB is the 13th leading cause of death and the second infectious killer after COVID-19 (above HIV/AIDS) worldwide (WHO, 2022).

Prevalence: In 2020, the notification rate in EU/EEA in 2020 was 7.3 per 100,000 population. Ten (10) countries reported 87.7% of the total cases, with Romania accounting for 23.2% of all TB cases reported in 2020. There were around 3,800 TB deaths reported in the EU/EEA (0.8 deaths per 100,000) in 2020 (ECDC, 2022a).

Demographics of the population in the proposed indication and risk factors for the disease:
In 2021, of the 10.6 million people who fell ill with TB worldwide, 6 million were men, 3.4 million women and 1.2 million children (WHO, 2022).

In the EU/EEA, in 2020, the highest rate was observed in the 25 to 44 years age group (9.0 per 100,000 population). Of 31,551 new and relapse TB cases reported in 2020, 20,448 (64.8%) were in the age group between 25 and 64 years and 6,152 cases (19.5%) were in adults aged >64 years. Rates were similar among the 15–24 and 45–64 years age groups (7.8 and 7.9 per 100,000 population, respectively), slightly higher among the 25–44 years age group (9.0 per 100,000 population) and slightly lower among those aged >64 years (6.6 per 100,000 population) (ECDC, 2022a). There was variation in the age distribution of cases between countries. In most countries, the cases were predominantly in patients between 25 and 64 years, but patients were younger in Malta (42.9% between 15 and 24 years), and older in Croatia, Estonia, Finland and Slovenia (where over 30% of patients were aged over 64 years (ECDC, 2022a).

Children <15 years accounted for 1,218 (3.8%) of 31,551 new and relapse TB cases reported in 2020. Children aged between 5 and 14 years had the lowest rate of all age groups, 1.5 per 100,000 population. Malta reported the highest rates among children < 15 years: 16.7 cases per 100,000 children aged 0 - 4, and 6.6 cases per 100,000 in children aged 5 - 14 (ECDC, 2022a).

In the EU/EEA in 2020, the male-to-female ratio in new and relapse TB cases was 2:1. In 26 of 29 EU/EEA Member States, more new and relapse TB cases were reported among males than females (ECDC, 2022a).

Globally, among all incident cases of TB in 2021, 6.7% were people living with HIV. The WHO African and South-East Asia regions accounted for 82% of the combined total of TB deaths in HIV-negative and HIV-positive people; India accounted for 32% of such deaths (WHO, 2022).

In the EU/EEA, HIV prevalence in incident TB cases was estimated to be 12% in 2020. There were an estimated 29,000 HIV-positive TB cases in the region, with almost 80% of cases estimated in the Russian Federation (55%) and Ukraine (24%). HIV status was reported for 12,327 (73.4%) of 16,804 TB cases reported from the 19 EU/EEA countries that reported HIV status of TB cases. Of the cases with known HIV status, 515 (4.2%) were reported as HIV-positive. Among the 15 countries with at least 50% reporting completeness for HIV status, the proportion of coinfected cases was highest in Estonia (9.7%), Hungary (11.8%) and Portugal (9.9%). The trend in the proportion of HIV-coinfected TB cases decreased from 4.5% in 2016 to 4.2% in 2020, but the proportion of coinfected cases in 2020 was higher than in 2019 (3.9%) (ECDC, 2022a).

A total of 1.6 million people died from TB in 2021 (including 187,000 people with HIV) worldwide. Of the global TB deaths among HIV-negative people in 2021, 54% were in men, 32% were in women and 14% were in children (aged <15 years). Of the global TB deaths among HIV-positive people, 51% were in men, 38% were in women and 11% were in children (WHO, 2022). In 2020, there were 3,800 TB deaths reported in the EU/EEA (0.8 deaths per 100,000) (ECDC, 2022a). An estimated number of 21,000 TB deaths occurred among HIV-negative people in the European Region in 2020, equivalent to 2.3 deaths per 100,000 population (range 2.2 - 2.4) (ECDC, 2022b).

The main existing diagnosis options:

Currently, the only way to diagnose a latent Mtb infection is detection of a host immune response to Mtb-derived antigens and thus, indirectly prove the (prior or present) presence of the bacteria. This approach is termed immune-diagnosis and the methods using this, like SIILTIBCY and the tuberculin skin test (TST), are called immune-based diagnostics.

The TST has been used during the last century for diagnosis of Mtb infection, and the purified protein derivative (PPD) TST is still one of the most important tools for diagnosis of latent TB. TST is easy to use and requires only a basic level of infrastructure and facilities, and the same procedure is applicable for both adults and children. However, TST has the disadvantage of low specificity and can give rise to false-positive reactions in individuals infected with non-tuberculosis mycobacteria and individuals vaccinated with Bacillus Calmette-Guérin (BCG) vaccines, because the PPD which is currently used is a heterogeneous mixture of antigens derived from Mtb, including antigens present in BCG vaccines. SIILTIBCY contains purified proteins specific of Mtb, namely a recombinant dimer of the 6 kDa early secretory antigen target (rdESAT-6) and a recombinant 10 kDa culture filtrate protein (rCFP-10).

During recent years, two commercially available *in vitro* immunodiagnostic assays (using wholeblood samples) – QuantiFERON®-TB Gold In-Tube Test (QFT; Qiagen) and T.SPOT®.TB (Oxford immunotec) – have been introduced in the diagnosis armamentarium ofDK Mtb infection. These use the similar recombinant antigens for diagnosis of Mtb infection as SIILTIBCY, i.e. ESAT-6, CFP-10 and TB7.7 in QFT and ESAT-6 and CFP-10 in T.SPOT®.TB. These assays are termed interferon-gamma release assays (IGRAs), as they quantitatively analyse the interferon-gamma release from T lymphocytes in the blood sample after this was exposed to the antigens. These two assays have shown a high specificity in BCG-vaccinated populations of >95% (Mori, 2004; Johnson *et al.,* 1999; Brock *et al.,* 2001), with sensitivity similar to TST (Mori T, 2009).

Natural history of the indicated condition in the untreated population, including mortality and morbidity:
Mtb normally enters the host by inhalation of infectious droplets from a contagious individual. In the lungs, the bacteria are taken up by phagocytic cells, but as a key feature of Mtb infection, the bacteria are able to survive and undergo progressive growth inside these cells. If the Mtb infection is not successfully contained by the host, typical symptoms of active TB disease will develop. Roughly estimated, the lifetime risk in infected individuals of developing active TB disease is around 5-15% (Vynnycky *et al.*, 2000). Individuals with HIV infection have an 18x higher risk of developing TB than HIV-negative individuals (WHO, 2022). Patients under immunosuppressive treatment are at a 3-20x higher risk of TB reactivation compared to the general population (Hasan *et al.*, 2018).

In the absence of clinically active TB disease, an Mtb infected individual is said to be latently infected or synonymously to have latent TB. This is important, as latently infected individuals form a vast pool of infected individuals from which new contagious TB cases continually will arise.

In adults and older children (over 5 years) the loss of containment gives rise to the typical symptoms – in particular a persistent cough with blood in the sputum. Infants and younger children (below 5 years) are less likely to develop these typical symptoms and thus, clinical diagnosis of TB disease in these younger children is difficult. This is an unfortunate problem, as at the same time, infants and younger children are at greater risk of a rapidly disseminating disease. Disseminated TB is a life-threatening condition defined as the presence of two or more non-contiguous sites resulting from hematogenous dissemination of Mtb infection to several organs (Khan, 2019).

Both with latent infection or TB disease, the infected individual's T-cells will be responsive to the Mtb-derived antigens used in the SIILTIBCY skin test, and a positive SIILTIBCY test result represents infection with Mtb at any place in the spectrum between latent infection and active TB disease. Identifying and appropriately treating Mtb infected individuals is one of the great challenges in TB control, and a pivotal point of rationale for the use of SIILTIBCY. Latently infected individuals form a vast pool of infected individuals from which new contagious TB cases continually will arise.

In all cases where Mtb infection is suspected, the presence of active TB disease will be evaluated. The initial approach will typically be the investigation for clinical symptoms, and in the absence of these, TB disease will generally be ruled out. In the case that relevant symptoms are present, further investigations typically include chest x-ray and sputum smear microscopy, and diagnosis is in general considered confirmed by detection of the bacteria by positive culture or polymerase chain reaction (PCR).

Unlike the diagnosis of active TB disease, diagnosis of a latent Mtb infection is more challenging. A latently infected person is typically asymptomatic, most often without radiological signs, and direct detection of the bacteria is not possible. Currently, the only way to diagnose a latent Mtb infection is detection of a host immune response to Mtb-derived antigens and thus, indirectly prove the (prior or present) presence of the bacteria with immunodiagnostics.

Important co-morbidities:
People living with HIV including those receiving antiretroviral therapy (ART), have an 18x higher risk of developing TB than HIV-negative individuals (WHO, 2022). In individuals infected with HIV-1, co-infection with TB is the leading cause of death. It is known that HIV-1 infection alters the course of Mtb infection and substantially increases the risk of active TB. TB increases levels of HIV-1 replication, propagation and genetic diversity (Bell *et al.*, 2018).

Active TB disease develops in approximately 5% of Mtb-infected individuals within two years. The innate immune response through B cells and the antibodies mediate Mtb killing directly through stimulation of antigen presentation, and cytokine production aimed at enhanced killing of Mtb infected macrophages. Quantitative and qualitative depletion of CD4 T-cells during HIV infection increases the risk of Mtb disease. This immunologic impairment is associated with impaired granuloma formation, compromised Mtb containment and increasing bacillary burden. In turn, TB enhances HIV viral replication by increasing expression of viral growth receptors such as CXCR4 (Letang *et al.*, 2020).

In addition, the diagnosis of TB remains challenging in HIV co-infected individuals, due to a high frequency of smear-negative disease and high rates of extrapulmonary TB (Mendez-Samperio, 2020).

Part II: Module SII - Non-clinical part of the safety specification

The Good Laboratory Practice (GLP) studies were conducted between 2005 and 2008 according to existing guideline (ICH S6 (R1), 1997), revised in 2011.

Pharmacodynamics studies investigating the induction of pronounced induration and erythema were conducted in guinea pigs. These animals are the most commonly used models for skin sensitisation tests. Safety assessments were studied in naïve guinea pigs, mice, rats, and dogs due to the proven suitability of those animals in these types of studies.

Except for a single dose-toxicity study and a dose- and route-finding pilot study for embryo-foetal development, all toxicology studies were conducted in accordance with GLP and Note for Guidance on preclinical pharmacological and toxicological testing of vaccines (CPMP/SWP/465/95). Furthermore, the studies were performed in compliance with the OECD Principles of Good Laboratory Practice (as revised in 1997), as required by the Danish Medicines Agency Executive Order No 1245 of 12 December 2005 on GLP for Medicinal Products. These Principles are in conformity with other international GLP regulations.

The first non-clinical studies were performed with rdESAT-6 alone, and after further development, rCFP-10 was included in combination with rdESAT-6 in the product hereafter called SIILTIBCY. The design of the repeated-dose toxicity study was discussed and agreed on during a Scientific Advice Meeting with the Danish Medicines Agency in 2007. Local tolerance has been investigated as part of the repeated-dose toxicity and embryo-foetal toxicity studies.

During formulation development, phenol was included as preservative. The to-be-marketed formulation contains 0.5% phenol. All toxicity studies were conducted with unpreserved rdESAT-6 and SIILTIBCY(rdESAT-6 + rCFP-10), with the exception of a bridging repeated-dose embryo-foetal development study in which phenol-preserved SIILTIBCY was used. The bridging strategy was discussed and agreed on during Scientific Advices with the Paul-Ehrlich-Institut in 2011 (PEI, 2011) and the European Medicines Agency in 2012 (EMA, 2012).

An overview of the GLP studies performed using rdESAT-6, rCFP-10 and SIILTIBCY are shown in Table SII.1. In addition, the non-GLP studies performed using rdESAT-6 and SIILTIBCYare summarized in Table SII.2.

Table SII.1: An overview of the GLP studies carried out with rdESAT-6, rCFP-10 and SIILTIBCY

Type of study	Species and strain	Route	No. of animals per gender/group	Duration of dosing	Doses (µg/animal)	HED (µg/Kg)
Single-dose toxicity of rdESAT-6	Mouse/Bom: NMRI	i.v.	Test: 12 M, 12 F Control: 12 M, 12 F	Day 1	0, 100	327.07
Single-dose toxicity of rdESAT-6	Rat/HsdBrlHan:WIST	s.c.	Test: 12 M, 12 F Control: 12 M, 12 F	Day 1	0, 1000	344.94
Repeated-dose toxicity of rdESAT-6	Rat/HsdBrlHan:WIST	s.c.	Test: 10+10+15 M, 10+10+15 F Control: 15 M, 15 F	Days 1, 8, 15 and 22	0, 1, 10, 100	6.87
Repeated-dose toxicity of rdESAT-6 and SIILTIBCY (rdESAT-6 + rCFP-10)	Rat, Wistar (Crl:WI(WU))	s.c.	Test: 15 M, 15 F Control: 15 M, 15 F	Days 0, 7, 14 and 21	0, 10 (rdESAT-6), 10 (5 + 5) (SIILTIBCY)	4.63 (rdESAT-6) 4.64 (SIILTIBCY)
Repeated-dose toxicity of rdESAT-6	Dog, Beagle	s.c.	Test: 2 M+2 M	Days 1, 8, 15 and 22	10, 100	0.61
Embryo-foetal developmental toxicity of SIILTIBCY (rdESAT-6 + rCFP-10)	Rat, Wistar (RccHan:WIST)	s.c.	Test: 28 F Control: 26 F	Days -14, 0, 6 and 13	0, 10 (5 + 5)	6.08
Local tolerance of rdESAT-6 and SIILTIBCY (rdESAT-6 + rCFP-10)	Rat, Wistar (Crl:WI(WU))	s.c.	Test: 15 M, 15 F Control: 15 M, 15 F	Days 0, 7, 14 and 21	0, 10 (rdESAT-6), 10 (5 + 5) (SIILTIBCY)	Not calculated
Local tolerance of SIILTIBCY (rdESAT-6 + rCFP-10)	Rat, Wistar (RccHan:WIST)	s.c.	Test: 28 F Control: 28 F	Days -14, 0, 6 and 13	0, 10 (5 + 5)	Not calculated

M, male, F, female, i.v., intravenous, s.c., subcutaneous, HED, human equivalent dose.

Table SII.2: An overview of the non-GLP studies carried out with rdESAT-6, rCFP-10 and SIILTIBCY

Type of study	Species and strain	Route	No. of animals per gender/group	Duration of dosing	Doses, µg/animal
Dose-response and toxicology of rdESAT-6 in infected guinea pigs	Dunkin Hartley guinea pigs	i.d.	Test: 6 F	Day 28 after infection	0, 0.010, 0.046, 0.215, 1.000
Dose-response of CFP10 and rdESAT-6 in infected guinea pigs	Dunkin Hartley guinea pigs	i.d.	Test: 6 F	Day 28 after infection	0.10, 0.46, 2.15, or 10.00 (rCFP-10), 0.010, 0.046, 0.215, or 1.000 (rdESAT-6)

Type of study	Species and strain	Route	No. of animals per gender/group	Duration of dosing	Doses, µg/animal
Dose-response of rdESAT-6 and SIILTIBCY in Mtb infected guinea pigs	Dunkin Hartley guinea pigs	i.d.	Test: 6 F Control: 2 F	Day 28 after infection	0.01, 0.1 or 1.0 (rdESAT-6), 0.01, 0.1 and 1.0 (rdESAT6 + rCFP-10 in 1:1 ratio)
Dose response of various mixtures of rdESAT-6 and CFP10 in Mtb infected guinea pigs	Dunkin Hartley guinea pigs	i.d.	Test: 6 F	Day 28 after infection	0.05 or 0.5 (rdESAT6 + rCFP-10 in various ratios), 10 TU PPD+ 0.16 (rdESAT6 + rCFP-10 in 1:1 ratios)
Sensitisation of guinea pigs with rdESAT-6	Dunkin Hartley guinea pigs	i.d.	Test: 6 F Control: 6 F	Days 0, 5, 10 and 24	10
Sensitisation of guinea pigs with rdESAT-6 or ESAT-6	Dunkin Hartley guinea pigs	i.d.	Test: 3 F Control: 3 F/group	Days 0, 24	1 (rdESAT-6), 1 (ESAT-6)
Sensitisation of guinea pigs with rdESAT-6 and CFP10	Dunkin Hartley guinea pigs	i.d.	Test: 3 F Control: 3 F	On 2nd, 4th or 8th week after first injection	1 or 10 (rdESAT-6 or rCFP-10)
Sensitisation of guinea pigs with rdESAT-6	Dunkin Hartley guinea pigs	i.d.	Test: 3 F	Day 0 and 14	1 (Standard rdESAT-6), 1 (rdESAT-6 ultrafiltered)
Sensitisation of guinea pigs with rdESAT-6 or rdESAT-6 + CFP10	Dunkin Hartley guinea pigs	i.d.	Test: 3 F Control: 3 F	Day 0 and 28	0, 1 (rdESAT-6), 1 (rdESAT-6 + rCFP10 mixed in the ratio of 1:1)
Skin reactions in guinea pigs of rdESAT-6 and CFP10 infected with various mycobacteria	Dunkin Hartley guinea	i.d.	Tests: 6 F	Day 28 after infection	1 (rdESAT-6), 1 (rCFP-10), 10 TU PPD
Potency of autoclaved rdESAT-6 in sensitised guinea pigs	Dunkin Hartley guinea pigs	i.d.	Test: 6 F	Day 28 after infection	0.04, 0.2 and 1.0 (rdESAT-6 stored at 2 - 8 °C or heated to 121 °C for 20 min)
Single-dose i.v. toxicity of rdESAT-6	Mouse/Bom:NMRI	i.v.	Test: 2 F Control: 2 F	Day 1	0, 1, 10, 100
S.c. or i.d. injection of SIILTIBCY (route finding study)	Rat, Wistar	i.d. and s.c.	Test: 3 F Control: 3 F	Day 0, 14, 20 and 28	0, 0.1 (s.c.), 10 (i.d. or s.c.)

F, female, i.d., intradermal, s.c. subcutaneous.

Key conclusions of the non-clinical programme

SIILTIBCY is an immunological recombinant medicinal product. It contains rdESAT-6 and rCFP10. Upon intradermal (i.d.) application in animals infected with Mtb, SIILTIBCY elicit delayed-type hypersensitivity (DTH) responses with erythema and induration at the injection site. rdESAT-10 and rCFP-10 provoked dose-dependent erythema in Mtb-infected guinea pigs but not in BCG-sensitised guinea pigs, demonstrating SIILTIBCY has the ability to discriminate infection with Mtb from previous vaccination with BCG. rdESAT-6 had almost 100-fold higher potency than rCFP-10 in Mtb-infected animals. The sensitivity was increased when rdESAT-6 and rCFP-10 are used in the ratio of 1:1. Therefore, the 1:1 ratio of both recombinant proteins was selected to be the optimal mixture of the final SIILTIBCY. SIILTIBCY may give a false positive result if an individual is tested twice four weeks apart. rdESAT-6 or SIILTIBCY did not induce a false positive skin reaction > 5 mm in naïve animals indicating that if SIILTIBCY administered to healthy human will not produce any undesired effect.

No toxicities have been recorded with rdESAT-6 and SIILTIBCY in animals at the estimated theoretical human equivalent doses (HED) at which no effects were observed of 6.87 µg/kg and 4.64 µg/kg (more than 2,700-fold higher than human dose), respectively in multiple-dose toxicity studies in animals. For all safety pharmacology variables analysed with rdESAT-6 and SIILTIBCY, i.e., electrocardiogram (ECG), respiratory pattern, ophthalmology, clinical chemistry, urinalysis, haematology and behavioural changes (Central Nervous System (CNS) effects), no treatment related effects were observed. SIILTIBCY did not show maternal and developmental toxicity in rats at the estimated HED where no effects were observed of 6.08 µg/kg (more than 3,500-fold higher than human dose). Only minor local reactions such as erythema, scaly skin and/or encrustation were observed at the sites of application.

In summary, preclinical data of SIILTIBCY reveals no special hazard for humans based on conventional studies of acute-dose toxicity, repeated-dose toxicity, and embryo-foetal development.

Part II: Module SIII - Clinical trial exposure

A tabular listing of the clinical trials is presented in Table SIII.1. A total of 3,109 participants were included in the clinical trial programme of SIILTIBCY, and an additional 66 subjects were included in the rdESAT-06 trials.

In total, 283 participants were exposed to SIILTIBCY alone, 2,577 participants were exposed to SIILTIBCY and PPD, 149 participants were exposed to PPD alone, 31 participants were exposed to rdESAT-6 alone and 35 participants were exposed to rdESAT-6 and PPD. The demographic profile of all participants of trials is summarised in Table SIII.2 and Table SIII.3.

Table SIII.1 Exposure in clinical trials included for safety assessment of SIILTIBCY

Trial ID	Age at Testing	Trial Name	Trial Population	Trial Drug/ Active Comparator	Safety Population
TESEC-01	18 to 55 years	An open phase I clinical trial on the safety and the risk of sensitisation by escalating doses and repeated injections of the rdESAT-6 + rCFP-10 skin test reagent following intradermal administration to healthy adults1.	Healthy, non-black, female/male adults with negative INF-γ response at inclusion (< 0.35 IU/mL) measured by QFT.	SIILTIBCY 0.01 µg/0.1 mL	**21**
				SIILTIBCY 0.1 µg/0.01 mL	**21**
TESEC-02	18 to 60 years	A safety and dose-finding trial of the diagnostic test C-Tb [SIILTIBCY], when given intradermally by the Mantoux technique to adult patients recently diagnosed with active TB2.	Female/male adults without HIV who were newly diagnosed with active TB and in treatment for ≤ 60 days at the time of inclusion. The participants had positive test results with either sputum smear microscopy, microbial culture, PCR or QFT.	SIILTIBCY 0.01 µg/0.1 mL (+/- 0.5% phenol)	**12**
				SIILTIBCY 0.1 µg/0.1 mL (+/- 0.5% phenol)	**26**
TESEC-03	18 to 65 years	A phase IIa specificity trial of the diagnostic agent C-Tb [SIILTIBCY], when given intradermally by the Mantoux technique to healthy volunteers previously vaccinated with BCG2.	Female/male BCG-vaccinated adults with negative INF-γ result at inclusion (< 0.35 IU/mL) measured by QFT.	SIILTIBCY 0.1 µg/0.1 mL + PPD	**151**
TESEC-04	18 to 64 years	A phase IIb sensitivity trial of the diagnostic agent C-Tb [SIILTIBCY], when given intradermally by the Mantoux technique to adult patients recently diagnosed with active TB3.	Female/male HIV-negative and HIV-positive adults with a recent diagnosis of active TB and in treatment for acute Mtb infection.	SIILTIBCY 0.1 µg/0.1 mL + PPD	**253**

Trial ID	Age at Testing	Trial Name	Trial Population	Trial Drug/ Active Comparator	Safety Population
TESEC-05	28 days to 65 years	A phase III trial in subjects suspected to have tuberculosis, comparing the diagnostic performance of C-Tb [SIILTIBCY] to QuantiFERON®-TB Gold In-Tube Test, in combination with a double-blind randomised split-body safety assessment of C-Tb [SIILTIBCY] versus 2 T.U. Tuberculin PPD RT 23 SSI (PPD).	Female/male HIV-negative and HIV-positive participants with suspicion of TB disease and HIV-negative children (5-11 years) with no symptoms of TB as negative control. Paediatrics: 28 days – 17 years of age Adults: 18 - 65 years of age	SIILTIBCY 0.1 µg/0.1 mL + PPD	**1190** (two participants only received PPD)
TESEC-06	6 weeks to 76 years	A phase III contact tracing trial comparing the diagnostic performance of C-Tb [SIILTIBCY] to QuantiFERON®-TB Gold In-Tube Test, in combination with a double-blind randomised split-body safety assessment of C-Tb [SIILTIBCY] versus 2 T.U. Tuberculin PPD RT 23 SSI[4].	Female/male HIV-negative and HIV-positive participants belonging to one of the following risk groups: Negative control Occasional contact to TB index case Close contact to TB index case Confirmed TB disease (positive control) Paediatrics: 6 weeks – 17 years of age Adults: 18 - 65 years of age	SIILTIBCY 0.1 µg/0.1 mL + PPD except for 50 participants in the negative control group, who received SIILTIBCY injection only as planned	**979** (one participant did not receive SIILTIBCY)
TESEC-07	18 to 67 years	A double-blind randomised phase II/III trial in adult patients recently diagnosed with active TB investigating if concomitant injections of the diagnostic agents C-Tb [SIILTIBCY] and 2 T.U Tuberculin PPD RT 23 SS affect the induration responses in combination with a safety assessment of C-Tb [SIILTIBCY].	Female/male HIV-negative and HIV-positive adults diagnosed with acute Mtb infection.	SIILTIBCY 0.1 µg/0.1 mL	**153**
				SIILTIBCY 0.01 µg/0.1 mL + PPD	**154**
				PPD	**149**
TESAT-01	19 to 58 years	A phase I (first-in-man), double-blind, "within-subject" randomised and controlled, dose-escalating clinical trial on the safety and the diagnostic potential of	Healthy adult men, who were QFT-negative.	rdESAT-6 0.01, 0.1, 1.0 and 10.0 µg/0.1mL 2 T.U. PPD	**20**

Trial ID	Age at Testing	Trial Name	Trial Population	Trial Drug/ Active Comparator	Safety Population
		the rdESAT-6 skin test in the diagnosis of tuberculosis.	Female/male adults, previous TB patients.	rdESAT-6 0.01, 0.1, 1.0 and 10.0 µg/0.1mL 2 T.U. PPD	**15**
TESAT-02	19 to 68 years	A phase I clinical trial to assess the risk of sensitisation in healthy adults following repeated administration of rdESAT-6 by the Mantoux injection technique.	Female/male healthy adult participants.	rdESAT-6 0.01 mg/mL	**31**
Total				SIILTIBCY	**3109**
				rdESAT-6	**66**

BCG = Bacillus Calmette-Guérin; HIV = human immunodeficiency virus; INF-γ = interferon gamma; Mtb = *Mycobacterium tuberculosis*; PCR = polymerase chain reaction; QFT = QuantiFERON®-TB Gold In-Tube test; TB = tuberculosis
[1] (Bergstedt *et al.*, 2010); [2] (Aggerbeck *et al.*, 2013); [3] (Hoff *et al.*, 2016); [4] (Ruhwald *et al.*, 2017)

Table SIII.2 Demographic profile of participants in SIILTIBCY +/- PPD trials

No. of participants	Treatment groups			Total
	SIILTIBCY N = 283	SIILTIBCY + PPD N = 2677	PPD N = 149	N = 3019
Age groups				
0-1 years	-	115	-	115
2-4 years	-	156	-	156
5-11 years	-	312	-	312
12-17 years	3	137	-	140
≥ 18 years	280	1957	149	2386
Sex				
Female	139	1332	48	1519
Male	144	1345	101	1590
Race				
African Origin	100	1008	96	1204
Asian	-	9	-	9
Black	38	247	37	322
Non-black	42	-	-	42
Unknown	38	-	-	38
White	50	980	-	1030
Other	15	433	16	464
HIV status				
HIV-positive	31	439	28	498
HIV-negative	218	1346	121	1685
unknown	34	892	0	926
BCG vaccination				
Yes	97	1525	93	1715
No	93	803	45	941
Unknown	93	349	11	453

BCG = Bacillus Calmette-Guérin; HIV = human immunodeficiency virus; N = total number of trial participants

Table SIII.3 Demographic profile of participants in rdESAT 6 +/- PPD trials

No. of participants	Treatment groups		Total
	rdESAT-6 N = 31	rdESAT-6 + PPD N = 35	N = 66
Age groups			
0-1 years	-	-	-
2-4 years	-	-	-
5-11 years	-	-	-
12-17 years	-	-	-
≥ 18 years	31	35	66
Sex			
Female	22	5	27
Male	9	30	39
Race			
African Origin	-	-	-
Asian	-	-	-
Black	-	-	-
Non-black	-	20	20
Unknown	31	15	46
White	-	-	-
Other	-	-	-
HIV status			
HIV-positive	-	-	-
HIV-negative	-	35	35
unknown	31	-	31
BCG vaccination			
Yes	-	4	4
No	-	16	16
Unknown	31	15	46

BCG = Bacillus Calmette-Guérin; HIV = human immunodeficiency virus; N = total number of trial participants

Part II: Module SIV - Populations not studied in clinical trials

SIV.1 Exclusion criteria in pivotal clinical studies within the development programme

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale:
Population with a disease affecting the lymphoid organs (e.g.	Active diseases affecting the lymphoid organs might affect the ability to form an	No	Impaired immune responses might affect the ability to form an

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale:
Hodgkin's disease, lymphoma, leukemia, sarcoidosis).	induration response to SIILTIBCY.		induration response to SIILTIBCY, leading to a false-negative test result. However, the safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Population who had within 3 months prior to the day of inclusion been in treatment with a product which is likely to modify the immune response except for HIV treatment (e.g., immunoglobulin, systemic corticosteroids, methotrexate, azathioprine, cyclosporine or blood products).	Immunocompromised participants may have impaired immune responses and might affect the ability to form an induration response to SIILTIBCY.	No	Immunosuppressants might affect the ability to form an induration response to SIILTIBCY, leading to a false-negative test result. However, the safety profile is not expected to be different in this population and there is not anticipated to be a significant impact on the benefit-risk profile.
Population with condition in which repeated blood drawings posed more than minimal risk for the volunteer, such as haemophilia, other coagulation disorders, or significantly impaired venous access.	Participants have a potential risk of hematoma due to the puncture of the deep tissues. Allowance of these conditions would confound assessment of safety.	No	It is common medical practice not to administer a product by the intradermal route in participants with coagulopathy or bleeding disorders although the use of a needle with proper gauge can decrease the risk.
Population who had been tuberculin (TST) tested < 12 months prior to the day of inclusion.	Because a recent testing with TST could boost the response of the comparator PPD RT 23 SSI.	No	Applicable for the comparator.
Pregnant, breastfeeding, or planning to become pregnant during the study.	Clinical development generally does not initially investigate benefit/risk in pregnant women.	No	No findings from non-clinical studies suggest possible concerns in pregnant or breastfeeding women. Animal studies have not apparently shown alterations of the foetus; moreover, systemic exposure of SIILTIBCY is negligible.

Criterion	Reason for exclusion	Is it considered to be included as missing information?	Rationale:
			No data are available on the presence of SIILTIBCY in human milk but, in consideration of the low systemic exposure, also for lactating women no important impact on breast-fed infants or on milk production is anticipated.

SIV.2 Limitations to detect adverse reactions in clinical trial development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or repeated exposure.

SIV.3 Limitations in respect to populations typically under-represented in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	
Patients with relevant comorbidities: Patients with hepatic impairment Patients with renal impairment Patients with cardiovascular impairment Immunocompromised patients Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development program.
Population with relevant different ethnic origin	Refer to Table SIII.2 and Table SIII.3 for exposure information by ethnic origin from the studies.
Subpopulations carrying relevant genetic polymorphisms	Not applicable

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

Marketing authorisation (MA) for Cy-Tb (product name of SIILTIBCY in India) has been granted in India on 09-May-2022 to Serum Institute of India Pvt. Ltd. (SII), a partner of Serum Life Science Europe GmbH; however, no doses of SII Cy-Tb have been distributed in the market till date and therefore no post-authorisation exposure data is available.

Part II: Module SVI - Additional EU requirements for the safety specification

Potential for misuse for illegal purposes

SIILTIBCY contains two purified proteins specific to Mtb serving as antigens to detect Mtb infection. The antigens are non-habit forming, non-narcotic and have no potential for misuse. There is no potential for recreational use.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

SVII.1.1. Risks not considered important for inclusion in the list of safety concerns in the RMP

Reason for not including an identified or potential risk in the list of safety concerns in the RMP:

Risks with minimal clinical impact on patients:

- Injection site reactions such as pruritus, pain, haematoma, rash, vesicles, erythema and swelling.
- Systemic adverse events including headache, dizziness, generalised pruritus, rash, myalgia, pyrexia, malaise and fatigue.

Other reasons for considering the risks not important:

- Anaphylactic reactions: This is considered as a potential risk since, as with any other drug, rarely allergic or hypersensitivity reactions could occur in individuals allergic / hypersensitive to any components of the product. However, no cases of anaphylaxis have been reported in clinical or non-clinical trials with SIILTIBCY.
- Medication errors: There is potential of medication errors with SIILTIBCY if not administered as per the instructions given in the package leaflet. An inaccurate test result due to inadvertent subcutaneous or intramuscular injection or on repeat testing below 6 weeks could lead to delayed or inappropriate treatment for TB. However, this is a preventable risk, and no cases of medication errors were observed in the clinical trials.

SVII.1.2. Risks considered important for inclusion in the list of safety concerns in the RMP

Important Identified Risks

Risks	Risk-benefit impact
None	Not Applicable

Important Potential Risks

Risks	Risk-benefit impact
None	Not Applicable

Missing information

Risks	Risk-benefit impact
None	Not Applicable

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

This section is not applicable as this is the initial RMP.

SVII.3 Details of important identified risks, important potential risks, and missing information

SVII.3.1. Presentation of important identified risks and important potential risks

Not applicable.

SVII.3.2. Presentation of the missing information

Not applicable.

Part II: Module SVIII - Summary of the safety concerns

Table SVIII.1: Summary of safety concerns

Important Identified Risk	• None
Important Potential Risk	• None
Missing information	• None

Part III: Pharmacovigilance Plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities are considered sufficient to monitor the safety profile of the product.

Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:

Specific adverse reaction follow-up questionnaires:

No specific adverse reaction follow-up questionnaires are proposed by the Marketing Authorisation Holder (MAH).

Other forms of routine pharmacovigilance activities:

None proposed.

III.2 Additional pharmacovigilance activities

Based on the various available clinical studies, SIILTIBCY was found to be safe and well tolerated.

The pooled safety analysis of SIILTIBCY, including data on 3,109 participants from 07 clinical trials (phase I – Denmark and UK, phase II – UK and South Africa and USA and phase III – Spain and South Africa), did not report any safety concern.

Therefore, no additional pharmacovigilance activities are proposed such as non-clinical, clinical or epidemiological (non-interventional or interventional) studies that are imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit/risk), specific obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances or required activities by the competent authority.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

Part IV: Plans for post-authorisation efficacy studies

There are no planned or on-going post-authorisation efficacy studies.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

There are no important potential or identified risks associated with SIILTIBCY. Routine risk minimisation measures are considered sufficient to manage the safety concerns of the medicinal product.

V.2. Additional Risk Minimisation Measures

No additional risk minimisation measures are required for SIILTIBCY. Routine risk minimisation activities as described in Part V.1 are sufficient to manage the safety concerns of the medicinal product.

V.3 Summary of risk minimisation measures

Not applicable.

Part VI: Summary of the risk management plan

Summary of risk management plan for SIILTIBCY (rdESAT-6 and rCFP-10)

This is a summary of the risk management plan (RMP) for SIILTIBCY (0.5 microgram + 0.5 microgram)/mL solution for injection (SIILTIBCY). The RMP details important risks of SIILTIBCY, how these risks can be minimized, and how more information will be obtained about SIILTIBCY's risks and uncertainties (missing information).
SIILTIBCY's summary of product characteristics (SmPC) and its package leaflet gives essential information to healthcare professionals and patients on how SIILTIBCY should be used.

This summary of the RMP for SIILTIBCY should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of SIILTIBCY's RMP.

I. The medicine and what it is used for

SIILTIBCY is indicated as a diagnostic aid for detection of *Mycobacterium tuberculosis* infection, including disease, in adults and children aged 28 days or older. This medicinal product is for diagnostic use only. It contains recombinant dimer of Mtb 6 kDa early secretory antigenic target (rdESAT-6) and recombinant 10 kDa culture filtrate protein of Mtb (rCFP-10) as the active substances and it is given intradermal injection using the Mantoux technique. The medicinal product is for diagnostic use only.
Further information about the evaluation of SIILTIBCY's benefits can be found in SIILTIBCY's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage https://www.ema.europa.eu/en/medicines.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of SIILTIBCY, together with measures to minimise such risks and the proposed studies for learning more about SIILTIBCY's risks, are outlined below.
Measures to minimise the risks identified for medicinal products are:

- Specific information, such as adverse reactions; posology and method of administration; contraindications; warnings and precautions, in the package leaflet addressed to healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of important risks and missing information

Important risks of SIILTIBCY are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of SIILTIBCY. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine).

Important Identified Risk	• None
Important Potential Risk	• None
Missing information	• None

II.B Summary of important risks

Not applicable.

II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of SIILTIBCY.

II.C.2 Other studies in post-authorisation development plan

There are no studies required for SIILTIBCY.

Part VII: Annexes

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable.

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

Not applicable.

Annex 7 - Other supporting data (including referenced material)

References

Aggerbeck H, Giemza R, Joshi P, et al. Randomised clinical trial investigating the specificity of a novel skin test (Cy-Tb) for diagnosis of M. tuberculosis infection. PLoS One. 2013 May 14;8(5):e64215.

Bell, L., Noursadeghi, M. Pathogenesis of HIV-1 and Mycobacterium tuberculosis co-infection. Nat Rev Microbiol 16, 80–90 (2018). https://doi.org/10.1038/nrmicro.2017.128

Bergstedt W, Tingskov PN, Thierry-Carstensen B, et al. First-in-man open clinical trial of a combined rdESAT-6 and rCFP-10 tuberculosis specific skin test reagent. PLoS One. 2010 Jun 25;5(6):e11277.

Brock I, Munk ME, Kok-Jensen A, Andersen P. Performance of whole blood IFN-gamma test for tuberculosis diagnosis based on PPD or the specific antigens ESAT-6 and CFP-10. Int J Tuberc Lung Dis. 2001 May;5(5):462-7.

European Centre for Disease Prevention and Control. Tuberculosis. In: ECDC. Surveillance and Monitoring in Europe Stockholm: ECDC; 2022a. Available online from: https://www.ecdc.europa.eu/sites/default/files/documents/tuberculosis-annual-epidemiological-report-2020_1.pdf

European Centre for Disease Prevention and Control. Tuberculosis. In: ECDC. Annual epidemiological report for 2020. Stockholm: ECDC; 2022b. Available online from: https://www.ecdc.europa.eu/sites/default/files/documents/tuberculosis-annual-epidemiological-report-2020_1.pdf

European Centre for Disease Prevention and Control. Tuberculosis. In: ECDC. Annual epidemiological report for 2019. Stockholm: ECDC; 2021. Available from: https://www.ecdc.europa.eu/sites/default/files/documents/AER-TB-2019.pdf

European Medicines Agency (EMA). 2012. Scientific Advice – Final advice letter.

Hasan T, Au E, Chen S, Tong A, Wong G. Screening and prevention for latent tuberculosis in immunosuppressed patients at risk for tuberculosis: a systematic review of clinical practice guidelines. BMJ Open. 2018 Sep 12;8(9):e022445. doi: 10.1136/bmjopen-2018-022445. PMID: 30209157; PMCID: PMC6144320.

Hoff ST, Peter JG, Theron G, et al. Sensitivity of Cy-Tb: a novel RD-1-specific skin test for the diagnosis of tuberculosis infection. Eur Respir J. 2016 Mar;47(3):919-28.

Johnson PD, Stuart RL, Grayson ML, et al. Tuberculin-purified protein derivative-, MPT-64-, and ESAT-6-stimulated gamma interferon responses in medical students before and after Mycobacterium bovis BCG vaccination and in patients with tuberculosis. Clin Diagn Lab Immunol. 1999 Nov;6(6):934-7.

Khan FY. Review of literature on disseminated tuberculosis with emphasis on the focused diagnostic workup. J Family Community Med. 2019 May-Aug;26(2):83-91. doi: 10.4103/jfcm.JFCM_106_18. PMID: 31143078; PMCID: PMC6515764.

Letang E, Ellis J, Naidoo K, Casas EC, Sánchez P, Hassan-Moosa R, Cresswell F, Miró JM, García-Basteiro AL. Tuberculosis-HIV Co-Infection: Progress and Challenges After Two Decades of Global Antiretroviral Treatment Roll-Out. Arch Bronconeumol. 2020 Jul;56(7):446-454. doi: 10.1016/j.arbr.2019.11.013. PMID: 35373756.

Méndez-Samperio, P. (2017), Diagnosis of Tuberculosis in HIV Co-infected Individuals: Current Status, Challenges and Opportunities for the Future. Scand J Immunol, 86: 76-82. https://doi.org/10.1111/sji.12567

Mori T, Sakatani M, Yamagishi F, et al. Specific detection of tuberculosis infection: an interferon-gamma-based assay using new antigens. Am J Respir Crit Care Med. 2004 Jul 1;170(1):59-64.

Mori T. Usefulness of interferon-gamma release assays for diagnosing TB infection and problems with these assays. J Infect Chemother. 2009 Jun;15(3):143-55.

Paul-Ehrlich-Institut (PEI). 2011. Scientific Advice.

Ruhwald M, Aggerbeck H, Gallardo RV, et al. Safety and efficacy of the Cy-Tb skin test to diagnose Mycobacterium tuberculosis infection, compared with an interferon γ release assay and the tuberculin skin test: a phase 3, double-blind, randomised, controlled trial. Lancet Respir Med. 2017 Apr;5(4):259-268.

Vynnycky E, Fine PE. Lifetime risks, incubation period, and serial interval of tuberculosis. Am J Epidemiol. 2000 Aug 1;152(3):247-63.

World Health Organization. Global Tuberculosis report 2022. Geneva; 2022. Available online from https://www.who.int/publications/i/item/9789240037021.