Programa Cooperación Farma-Biotech

8º encuentro (7 de mayo de 2013)

Ruti®: adjunctive immunotherapy to the standard antibiotic treatment for preventing tuberculosis in infected individuals

ARCHIVEL farma

Madrid, 7 de mayo de 2013

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES Plataforma Tecnológica Española

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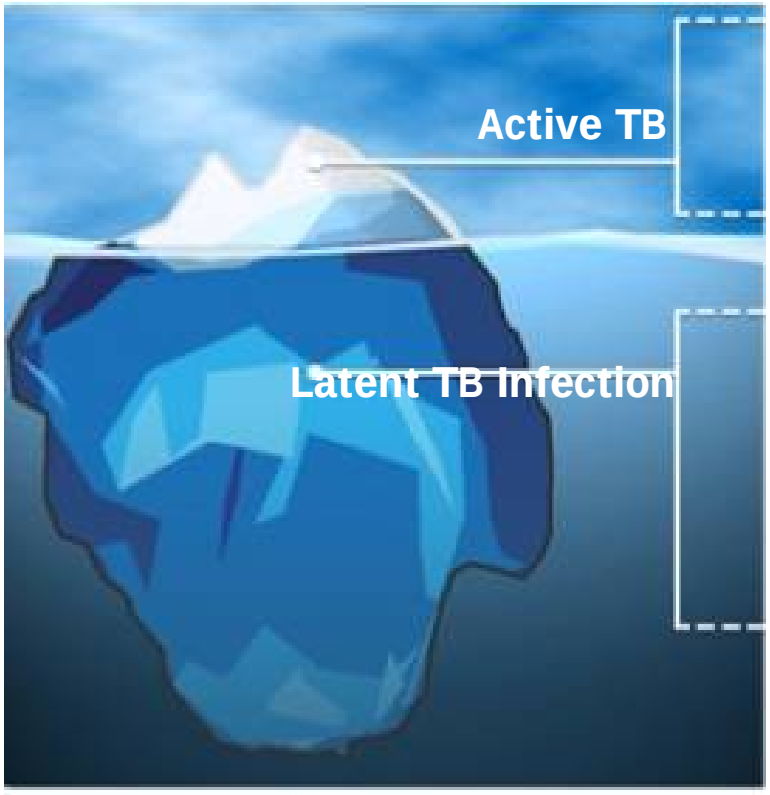
The problem to deal with

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

TB is a major global killer. Non-symptomatic, infected individuals constitute a huge reservoir currently non prioritized



- TB → second cause of death after AIDS
- 8.7 million new cases in 2011 (14% HIV+)
- 1.4 million deaths in 2011 – 1 every 20 seconds

- 1/3 of world population latently infected
- 100 million people infected every year
- Majority of infected people not aware
- 10% will develop active TB during their life

- Multidrug-Resistant and untreatable Tuberculosis on the rise
- Relapse and retreatment needs 30% cost

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1- The Company

- Private Biopharmaceutical company, created in 2005
- Located in Badalona, at 10 km Barcelona, Catalonia, Spain
- Own production plant + R&D facilities + P3 lab 720 m2
- STAFF: 20 employees + Chief Scientific Officer + Business developer

2. The RUTI® product

- A poly-antigenic therapeutic vaccine designed to prevent the development of active TB in individuals infected with *Mycobacterium tuberculosis* in combination with antibiotics
- Discovered at Institut Germans Trias i Pujol , Badalona, Spain ("Can Ruti")
- Made from *M. tuberculosis* grown under anoxic stress
- **Non live: fragmented, detoxified and liposomed**
- It generates a poliantigenic response against a wide range of antigens, including structural ones (latent bacilli)
- Lyophilized, stable at room temperature
- SC, single dose

2a. Main indication

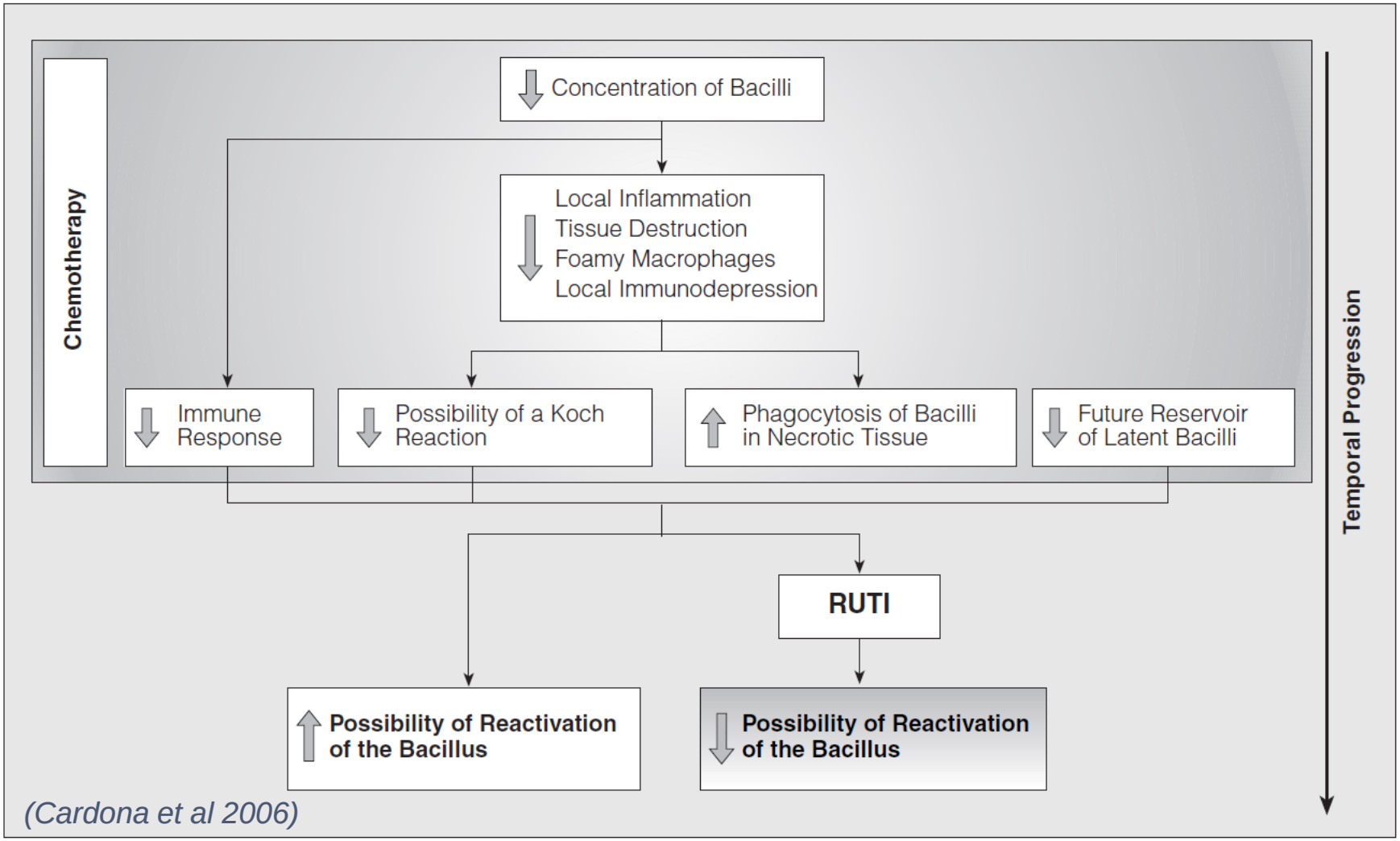
prevention of TB relapse

A phase III clinical trial to investigate safety and efficacy of the novel adjunctive immunotherapy RUTI administered to adults with drug-susceptible active TB who have completed two month of intensive phase plus the first month of continuation phase of active TB standard treatment

2a. Potential other applications of RUTI

- Adjunctive immunotherapy to antibiotic MDR treatment (short term: reduction of bacillary load in sputum; long term: reduction of active TB)
- First line therapy to prevent active TB in tuberculine and quantiferon negative subjects (close contacts)
- Adjunctive immunotherapy to prevent active tuberculosis in Latent Tuberculosis infected individuals at risk (i.e. HIV+ with LTBI) (*Study Protocol ready, to be implemented in South Africa subject to fund availability*)

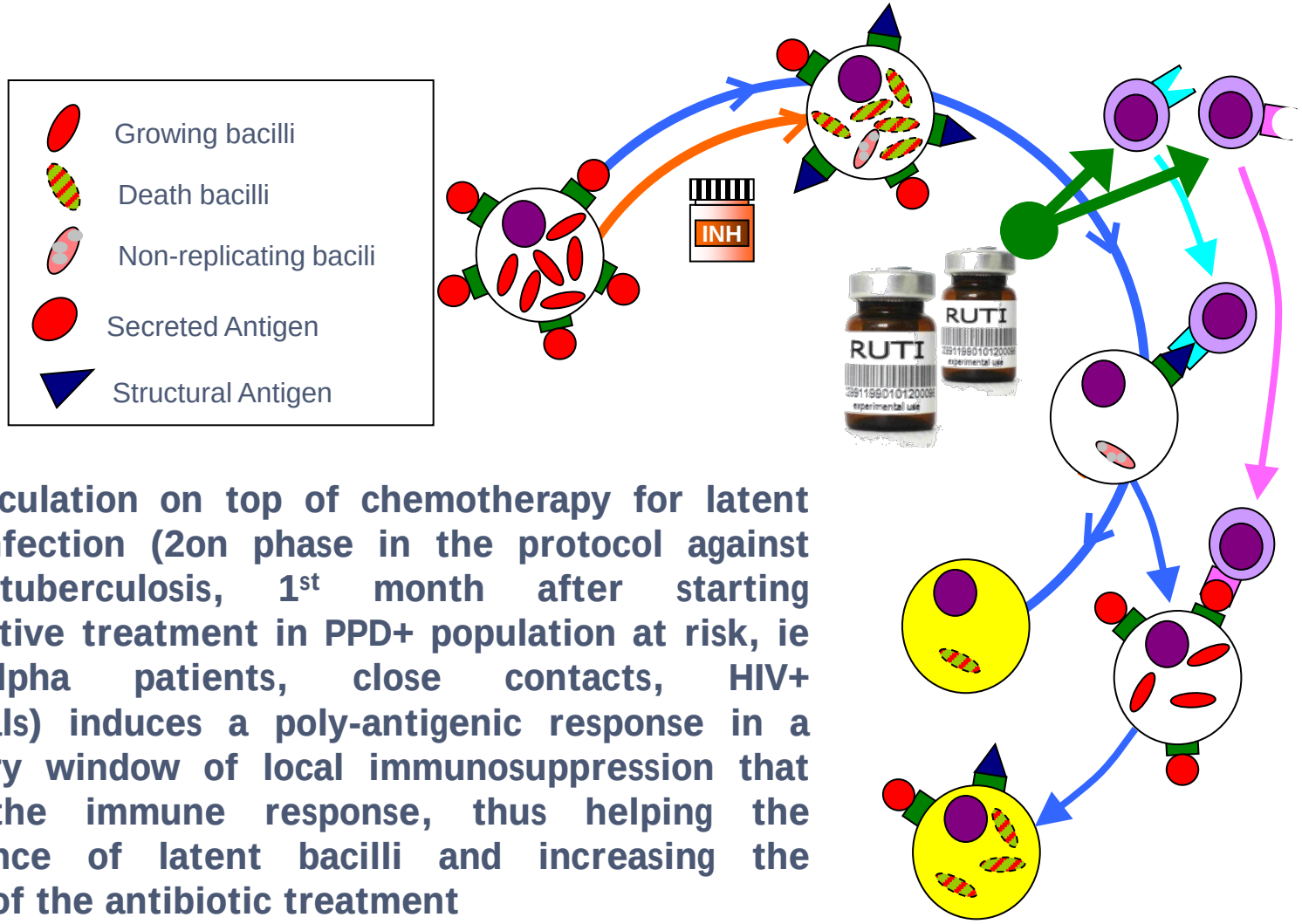
2b. Scientific hypothesis



(Cardona et al 2006)

Figure. Temporal strategy for the use of RUTI, indicating the effects of short-course chemotherapy and the requirement for subsequent immunotherapy.

2b. Mechanism of action



RUTI inoculation on top of chemotherapy for latent bacilli infection (2on phase in the protocol against active tuberculosis, 1st month after starting preventative treatment in PPD+ population at risk, ie antiTNFalpha patients, close contacts, HIV+ individuals) induces a poly-antigenic response in a temporary window of local immunosuppression that boosts the immune response, thus helping the surveillance of latent bacilli and increasing the efficacy of the antibiotic treatment

2c. Differential aspects facing the market

- First inmunotherapeutic approach to TB and first in combination to standard antibiotic therapy
- First inmunotherapeutic directed to INFECTED adults including HIV+
- Single dose, stable at room temperature
- **Polyantigenic** based on clinical isolate (the RUTI strain)

2c. Global TB Vaccine Pipeline

Phase I	Phase II	Phase IIb	Phase III
AdAg85A McMaster University	**M72+AS01** GSK, Aeras	**MVA85A/ AERAS-485 Oxford-Emergent Tuberculosis Consortium (OETC), Aeras, EDCTP, Wellcome Trust**	**Mw [M. indicus pranii (MIP)]** Dept of Biotechnology (India), M/s. Cadila
Hybrid-I+CAF01 SSI, TBVI	**VPM 1002** Max Planck, Vakzine Projekt Mgmt, TBVI	**AERAS-402/ Crucell Ad35** Crucell, Aeras, EDCTP, NIH	
H56+IC31 SSI, Aeras, Intercell	**Hybrid-1+IC31** SSI, TBVI, EDCTP, Intercell		
Hyvac 4/ AERAS-404 +IC31 SSI, sanofi-pasteur, Aeras, Intercell	**RUTI** Archivel Farma, S.L.		
ID93/GLA-SE IDRI, Aeras			

TB Vaccine Types
Viral-vectored: MVA85A, AERAS-402, AdAg85A
Protein/adjuvant: M72, Hybrid-1, Hyvac 4, H56
rBCG: VPM 1002, ID93/GLA-SE
Killed WC or Extract: Mw, RUTI

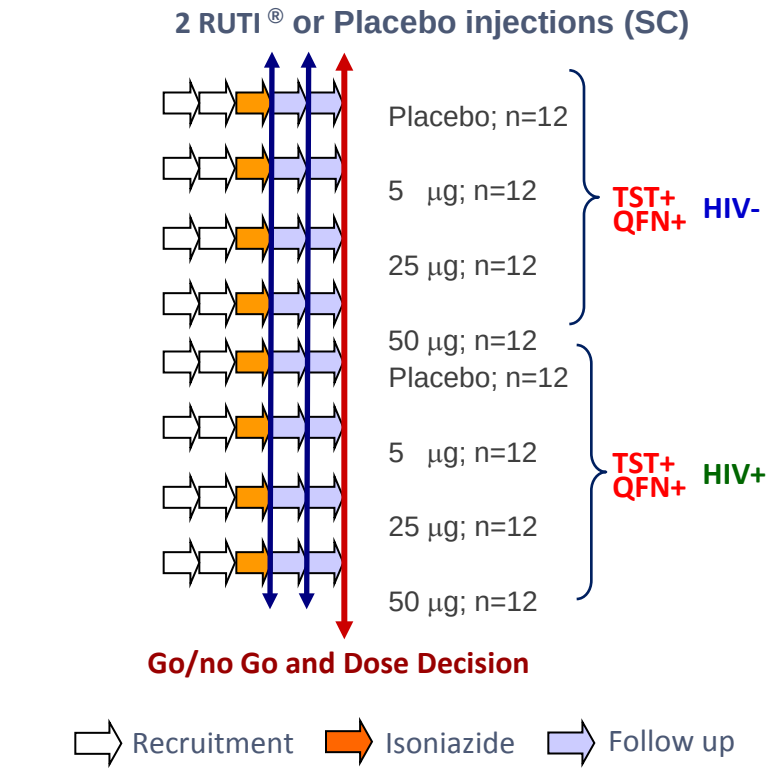
(P) Prime
(B) Boost
(PI) Post-infection
(IT) Immunotherapy

Source: Tuberculosis Vaccine Candidates – 2011

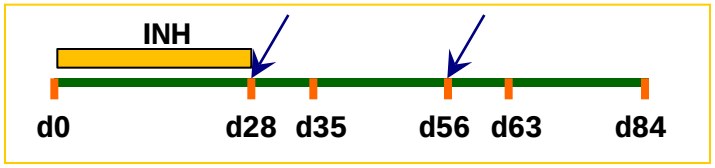
2d. Current status of development

- Phase II completed
- CMC development completed
- Current manufacturing capabilities up to 80M doses / year
- Two phase III trials designed
- EMA scientific advice validates strategy
- IP portfolio under review, first patent already granted most countries

Clinical Development – Phase II trial



- Trial started on June 2010
- Trial ended on July 2011
- 3 Clinical sites at Bluemfontain, George and Port Elisabeth; South Africa
- Safety, tolerability, monitored by an independent DSMC
- Immunogenicity and dose



http://clinicaltrials.gov/ct2/show/NCT01136161

Well tolerated dose and regime

Safety profile of 1 inoculation of RUTI 25 µg (n=12)

Systemic TEAE	Severity I n	Severity II n	Local TEAE	Severity I n	Severity II n
Malaise	1	1	**Pain**	6	1
			Erythema	9	1
			Swelling	7	2
			Induration	8	2
			Local nodule	6	1
			Vesicles	1	0

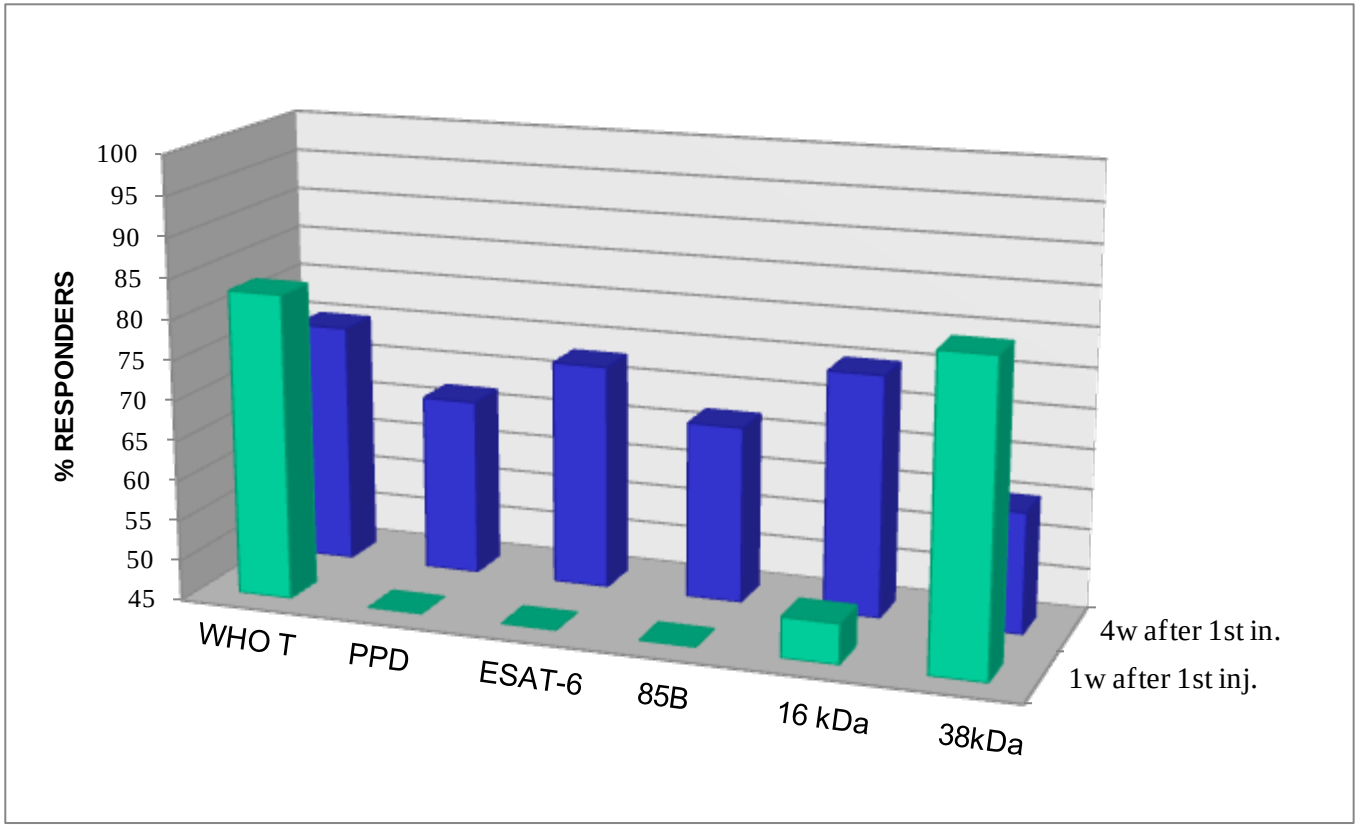
N: no. of subjects in the group;

n: no. of subjects reporting one or more treatment emergent adverse event

Severity: I Mild; II Moderate

Good poly-antigenic response

Immunological profile of 1 inoculation of RUTI 25 µg



% Responders (% of patients with values higher than median placebo)

Clinical Development – Phase II trial summary

- 96 LTBI subjects (48 HIV- and 48 HIV+)
- 3 doses tested
- Triggered a specific, poly-antigenic, cellular response even in the immunosuppressed HIV+ patients
- Single SC injection of 25 ug dose selected for phase III

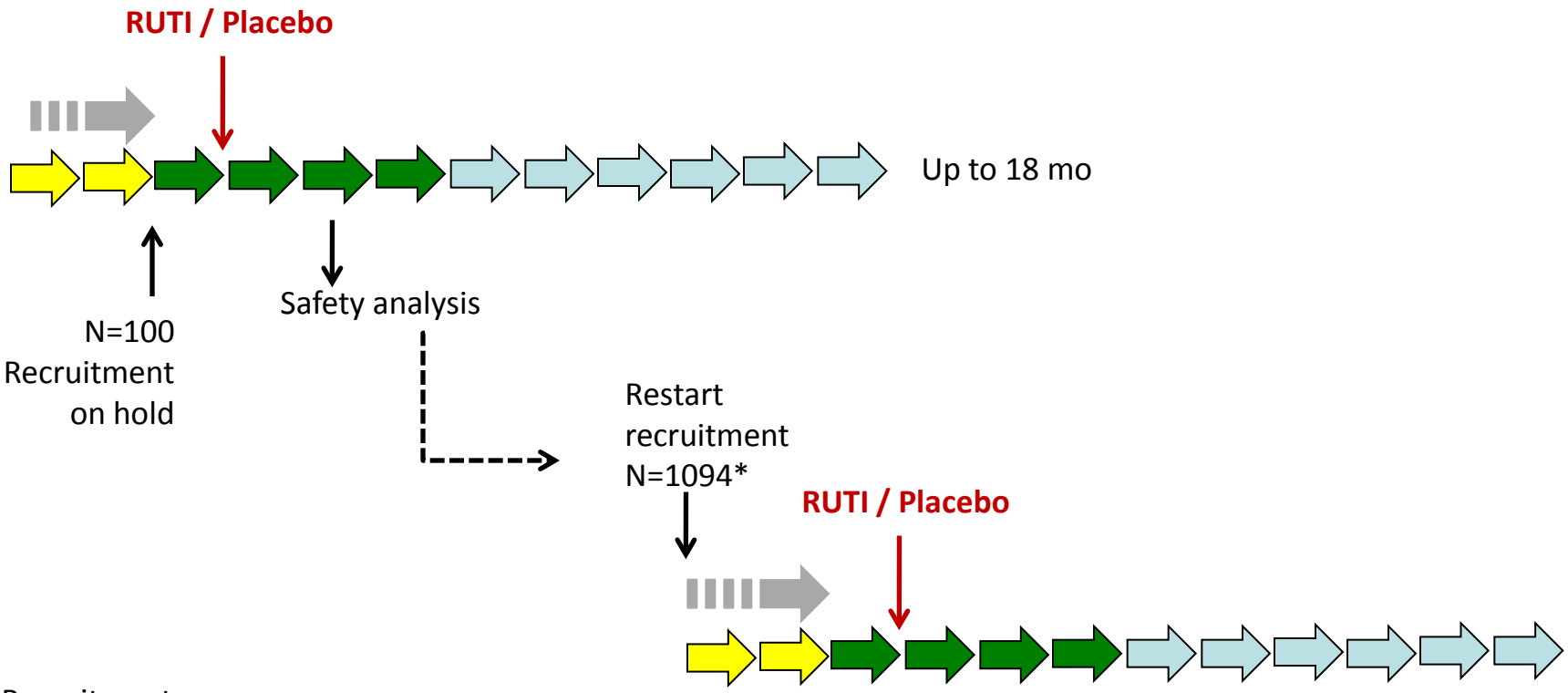
According to SAB, promising results that support progression to phase III

Phase III strategy for prevention of TB relapse

A phase III clinical trial to investigate safety and efficacy of the novel adjunctive immunotherapy RUTI administered to adults with drug-susceptible active TB who have completed two month of intensive phase plus the first month of continuation phase of active TB standard treatment

Phase III proposal for TB relapse

Single phase III trial including safety assessment of first 100 patients



- Recruitment
- Isoniazid, Rifampicin, Pyrazynamide, Ethambutol
- Isoniazid, Rifampicin
- One month follow up

**Assuming a 6% relapse incidence rate*

2d. Phase III proposal for TB relapse

Cost for a phase III trial as designed:

- In India: 3 M€ / 740 patients enrolled
- In South Africa: 7,6M€ / 1.194 patients enrolled

Calendar of phase III trial as designed: 32 months

Expected market entry (conditional approval): 2017-2018

2e. IP Portfolio

- WO2005/042013 granted in most countries, process, product and therapeutic uses
- WO2008/053055 granted in EU, national phases worldwide, prophylactic use
- PCT/ES2009/000436, entered national phases in Q1 2011, primary prophylactic use
- Patent application PCT/EP2012/050080 covering composition of matter of phase III product filed January 4th 2011
- International Application PCT/IB2012/000353, use of ruti in Asthma

2f. Pitfals and risks

- **Market access**
- **Lack of efficacy in phase III**
- *Manufacturing NOT an issue*
- *Cost of goods NOT an issue*
- *Generification NOT an issue*
- *Logistics NOT an issue*

Market potential

Market potential: active tuberculosis

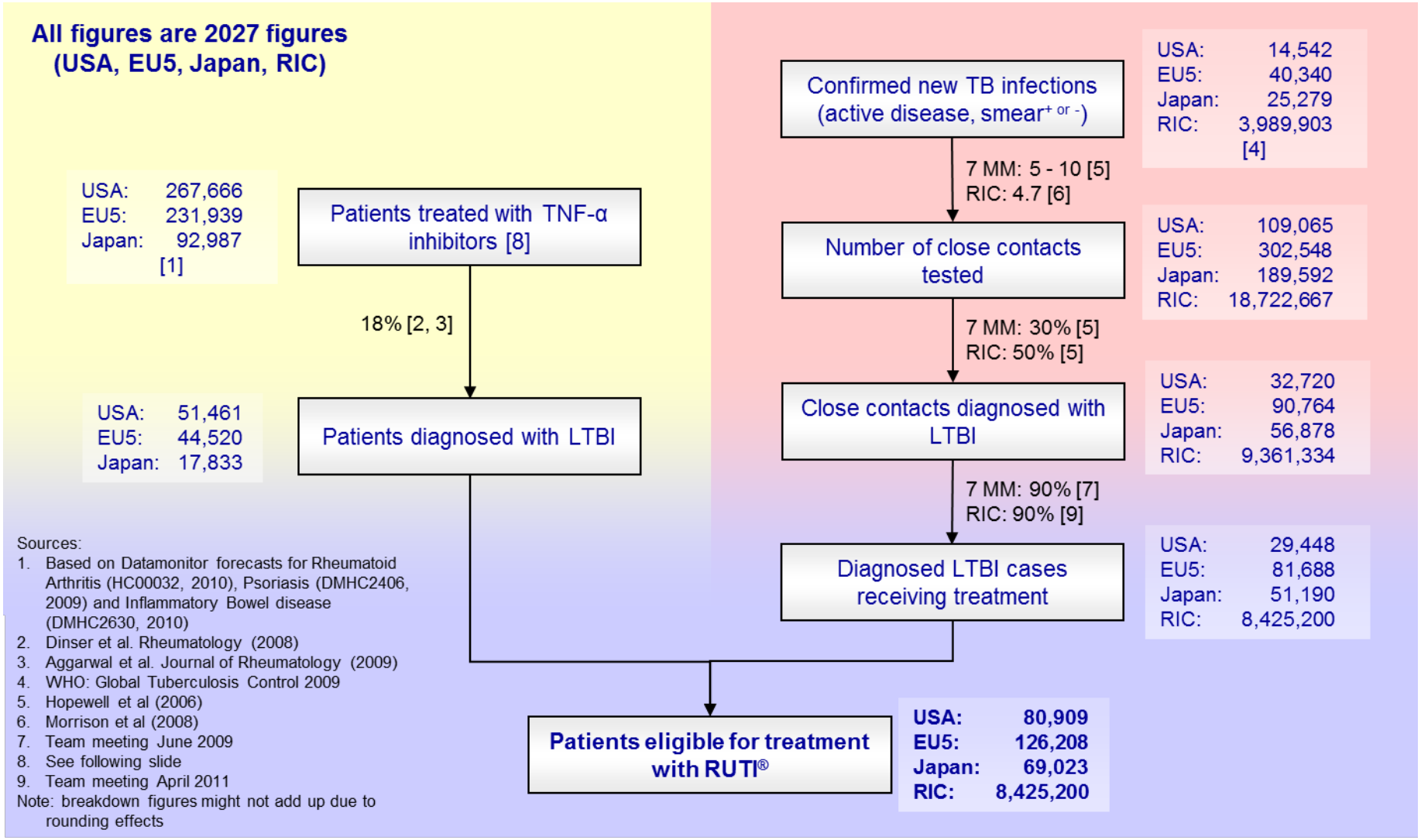
	PREVALENCE	INCIDENCE	NEW REPORTED CASES	RETREATMENTS	RELAPSES
INDIA	3.100.000	2.200.000	1.211.441	304.000	112.508
CHINA	1.400.000	1.000.000	865.059	46.825	34.610
BRASIL	91.000	83.000	71.337	10.045	3.555
RUSSIA	180.000	140.000	104.320	55.159	8.590
SOUTHAFRICA	390.000	500.000	325.321	45.915	18.394
SPAIN	8.700	7.200	6.044	370	0

Economic impact reduction in retreatment needs in India (worst case market scenario)

Direct cost of retreatment (ponderating 1st and 2nd line)	10% reduction	30% reduction	50% reduction
100€	4.623.140€	13.869.420€	23.115.700€
500€	23.115.700€	69.447.100€	115.578.500€

Market potential: latent tuberculosis

All figures are 2027 figures (USA, EU5, Japan, RIC)



Sources:

1. Based on Datamonitor forecasts for Rheumatoid Arthritis (HC00032, 2010), Psoriasis (DMHC2406, 2009) and Inflammatory Bowel disease (DMHC2630, 2010)
2. Dinser et al. Rheumatology (2008)
3. Aggarwal et al. Journal of Rheumatology (2009)
4. WHO: Global Tuberculosis Control 2009
5. Hopewell et al (2006)
6. Morrison et al (2008)
7. Team meeting June 2009
8. See following slide
9. Team meeting April 2011

Note: breakdown figures might not add up due to rounding effects

3. Looking for…

- Local development and commercial partners (China, India, Russia, Korea, East Europe, Other);

  OR

- Global development and commercial partner

Archivel is willing to share future benefits in exchange to financial and logistic support on a per-territory or global basis