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MESA-TB

Safety and immunogenicity of the investigational tuberculosis vaccine M72/AS01$_{E-4}$ in people living with HIV

Linda Han, MD, MPH

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The M72/AS01$_{E-4}$ investigational TB vaccine

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The M72/AS01E-4 TB vaccine candidate has been in development since the early 2000s, led by GSK (GlaxoSmithKline Biologicals, SA) up to the proof-of-concept Phase 2b trial

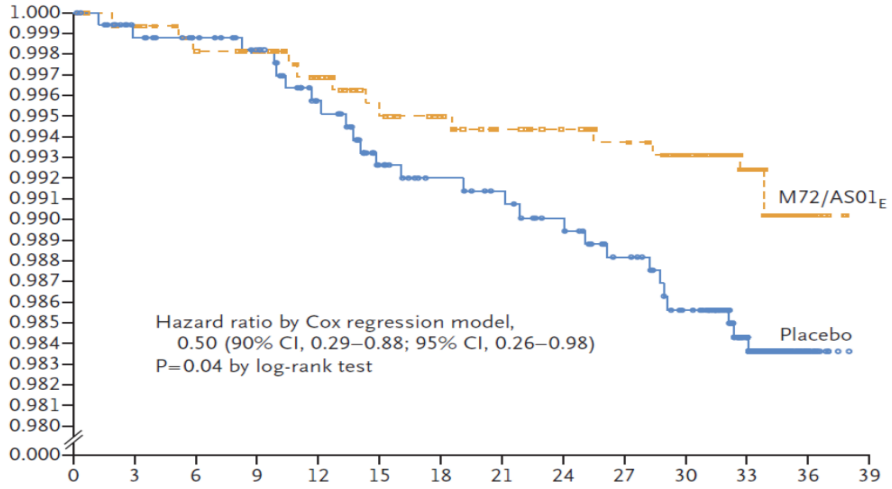
- The vaccine is comprised of
  - a recombinant fusion protein (M72) derived from 2 immunogenic *Mtb* antigens (Mtb39a and Mtb32a)
  - a GSK proprietary adjuvant system (AS01$_{E-4}$)
- GSK sponsored Phase 1 and 2 clinical trials of the vaccine in a range of populations and settings, including 2 trials in people living with HIV (PLHIV)

- Adults, PPD-positive, Philippines (TB-009)
- Adults, PPD-negative and -positive, S. Africa (TB-010)
- **Adults living with HIV, on anti-retroviral therapy (ART), Switzerland (TB-011)**
- Adolescents 13 to 17 years, S. Africa (TB-012)
- Healthy infants, Gambia (TB-013)
- **Adults living with HIV (on ART and ART-naïve), India (TB-014)**
- Healthy BCG-primed adults, Belgium (TB-019)

Phase 2b trial leading to Phase 3 plans

2018: GSK completed a Phase 2b trial of M72/AS01$_{E-4}$ for prevention of TB in ~3500 interferon gamma release assay (IGRA)-positive HIV-negative adults in Africa

- The vaccine efficacy against active pulmonary TB was 49.7% (95% CI: 2.1% to 74.2%) after all participants had completed 36 months of follow up
- No safety signals that would prevent further development



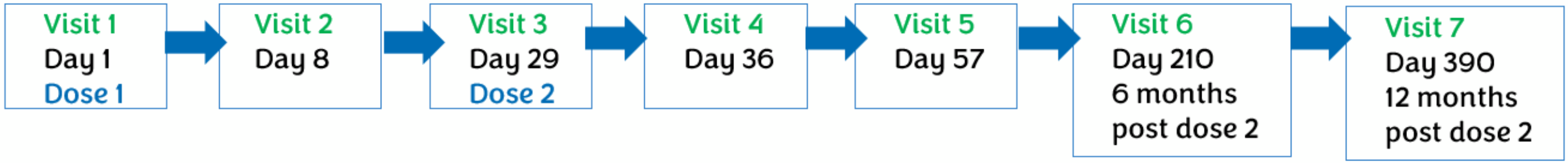
DOI: 10.1056/NEJMoa1803484 & DOI: 10.1056/NEJMoa1909953

2020: Gates MRI obtained a license from GSK to continue M72/AS01$_{E-4}$ development

- M72/AS01$_{E-4}$ clinical development plan includes
  - **Phase 2 trial in PLHIV in South Africa (MESA-TB)**(NCT04556981) to evaluate safety and immunogenicity in a larger population of PLHIV in a TB endemic region
  - Phase 3 vaccine efficacy trial

MESA-TB Trial Design

- Phase 2 randomized, observer-blind, placebo-controlled trial
- ~400 PLHIV, ages 16-35 years, at 6 sites in S. Africa
- Inclusion criteria included:
  - Antiretroviral therapy for ≥3 months
  - HIV viral load <200 copies/mL
  - CD4+ cell counts ≥200 cells/μL
  - TB preventive therapy in the past
  - No past/present history of TB
- Randomized 1:1 to M72/AS01$_{E-4}$ or saline placebo
  - Stratified by site and IGRA status
- Participants received 2 intramuscular doses, one month apart
- Followed through Day 390
- An independent data monitoring committee (IDMC) monitored the trial
- Trial began Nov 2020; ended Aug 2022



Trial objectives and endpoints

Solicited adverse events (AEs) (primary objective)	Recorded during the first 7 days after each dose • Injection site AEs: pain, redness, swelling • Systemic AEs: fever, headache, fatigue, myalgia
Unsolicited adverse events (AEs) (primary objective)	Recorded through 28 days after each dose
Serious AEs (primary objective)	Recorded through end of trial
Laboratory assessments	• Alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin • Hemoglobin, white blood cells, platelets • HIV viral loads • CD4+ T cell counts
Humoral immunogenicity	M72-specific antibody titers measured at Days 1, 29, 57, 210 and 390
Cellular immunogenicity	M72-specific CD4+/CD8+ T-cell responses measured by expression of IFN-γ or IL-2 using intracellular cytokine staining at Days 1, 57 and 390

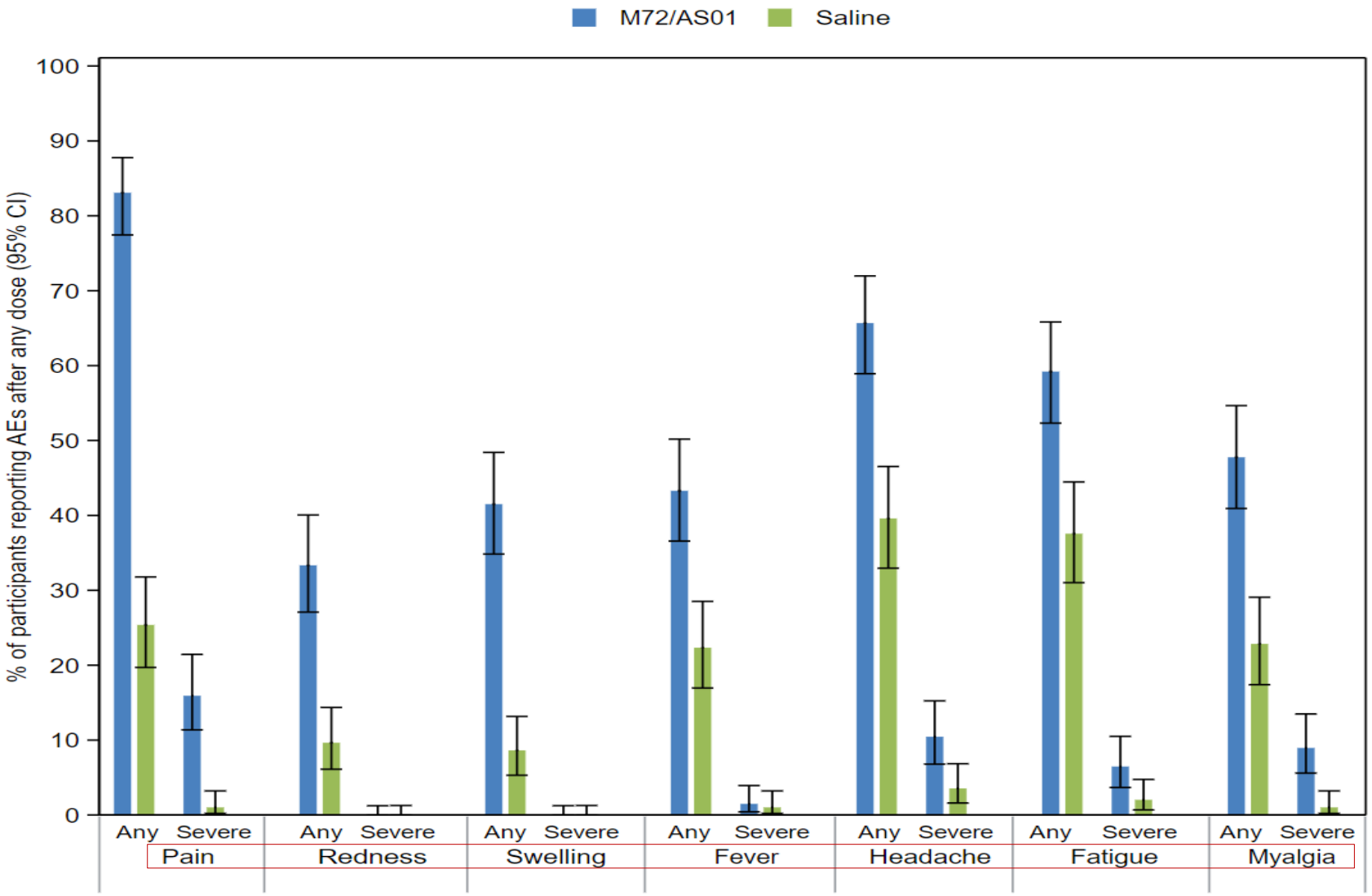
Disposition and demographics

Disposition	M72/AS01$_{E-4}$ n (%)	Placebo n (%)	Total n (%)
Randomized	202	200	402
Received at least one dose	201 (99.5)	200 (100.0)	401 (99.8)
Completed trial	195 (96.5)	181 (90.5)	376 (93.5)
Discontinued trial	7 (3.5)	19 (9.5)	26 (6.5)

Demographics

- Baseline characteristics were comparable between study groups
  (including age, sex, race, weight, height, body mass index, IGRA-status, CD4+ counts, HIV viral loads)
- Mean age was 30 years
- 88% of participants were women
- 48% of participants were IGRA-positive at baseline

Solicited and severe solicited adverse events



- Solicited AEs were more frequent in the M72/AS01$_{E-4}$ group
- Severe solicited AEs of pain, myalgia, and headache were more frequent in the M72/AS01$_{E-4}$ group
- Most AEs were mild to moderate severity; most resolved within 3 days

Severe solicited AEs defined as redness/swelling ≥100 mm, fever ≥39.3 to <40.0°C, and AEs preventing normal daily activities

Unsolicited and overall adverse events

	M72/AS01$_{E-4}$ (N = 201)		Placebo (N = 200)	
	n (%)	95% CI	n (%)	95% CI
Unsolicited AEs	94 (**46.8**)	39.9, 53.7	87 (**43.5**)	36.7, 50.4
Related unsolicited AEs	25 (**12.4**)	8.4, 17.6	11 (**5.5**)	2.9, 9.4
Severe related unsolicited AEs	2 (1.0)	0.2, 3.2	2 (1.0)	0.2, 3.3
SAEs	4 (2.0)	0.6, 4.7	5 (2.5)	0.9, 5.5
SAEs with outcome of death	0 (0.0)	-	1 (0.5)	0.0, 2.4

- % of participants with **unsolicited AEs** were similar between groups, overall and by severity
- **Related unsolicited AEs**, as determined by the principal investigators, were more frequent in the M72/AS01$_{E-4,}$group. The most common related AEs were:
  - injection site redness (7 in M72; 1 in placebo)
  - injection site itching (5 in M72, 1 in placebo)
  - dizziness (6 in M72; 5 in placebo)
  - injection site swelling (3 in M72, 0 in placebo)
- No differences between groups in SAEs

Laboratory assessments

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Safety lab assessments grade 3 or above

- No clinically meaningful differences in hematology and serum chemistry between groups

HIV viral loads

- No significant differences between groups at any post-baseline visit

CD4+ T cell counts

- % of participants with CD4+ T cell counts <350 x 10^6/L were similar between groups at all time points

IDMC reviews

At each quarterly meeting, the IDMC reviewed unblinded safety data and concluded that the trial could continue without modification.

Humoral and cellular immune responses peaked after dose 2 and were sustained at Day 390

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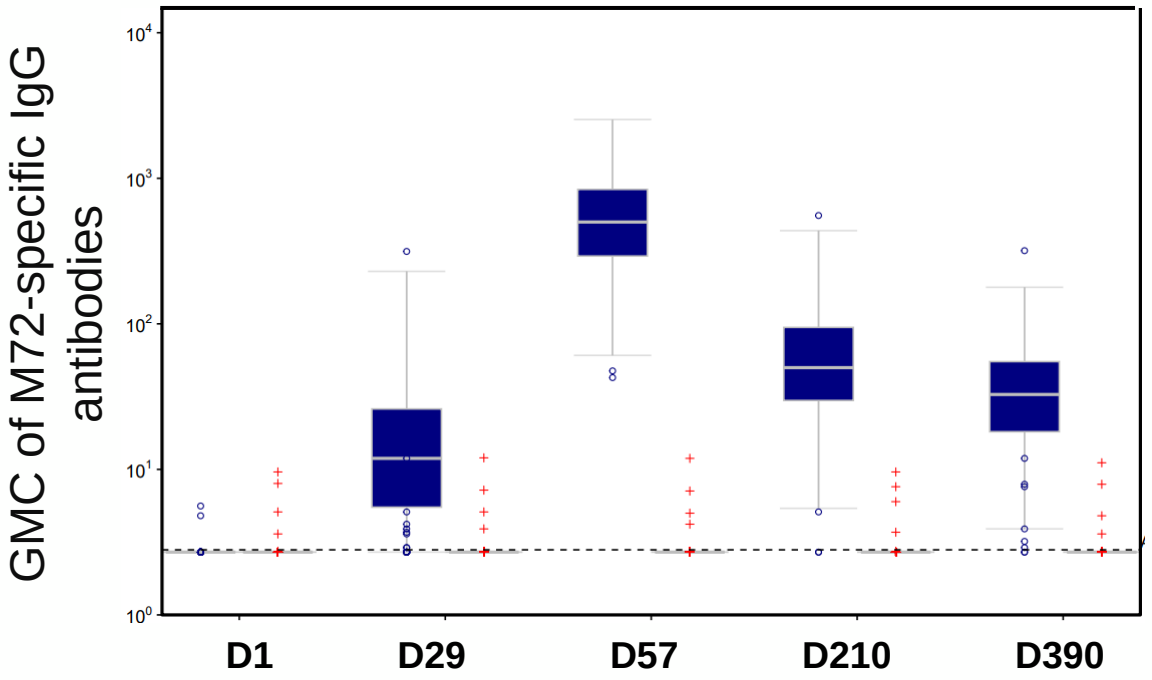
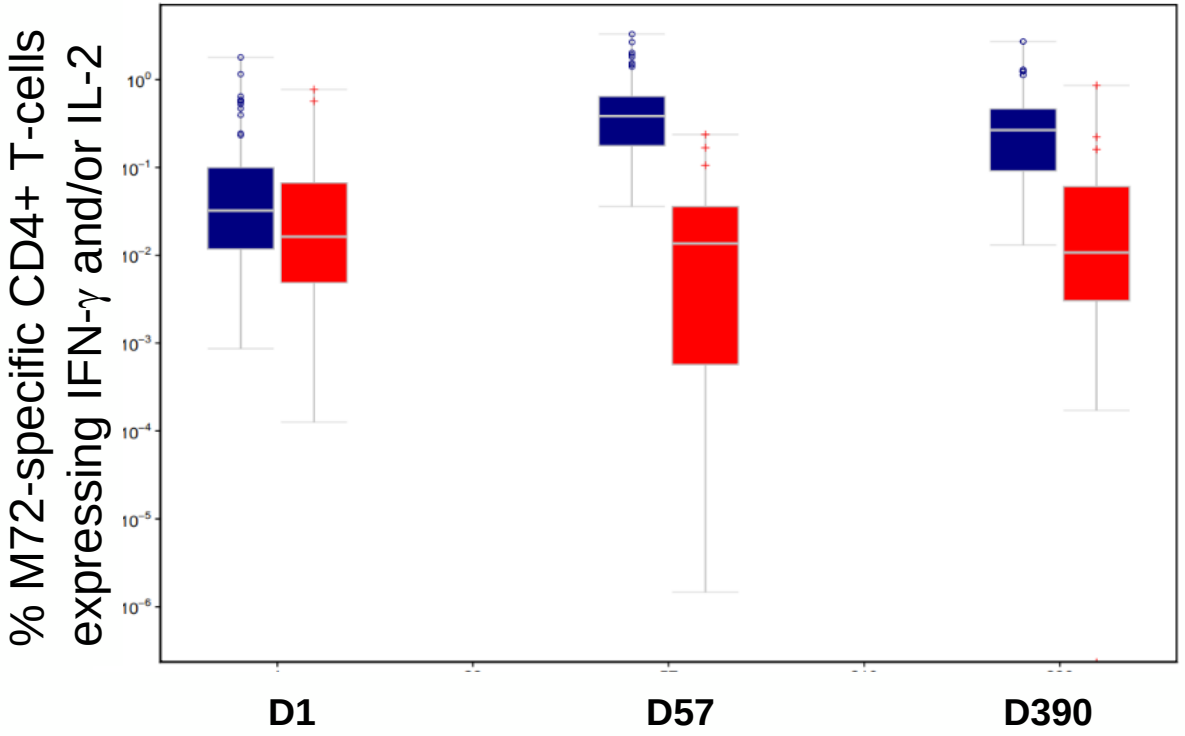
Humoral immune response



Cellular immune response



D = Day

M72/AS01E

Saline Placebo

Conclusion

A 2-dose regimen of M72/AS01$_{E-4}$ vaccine, administered 1 month apart, was well-tolerated with no safety signals, and was immunogenic in virally suppressed, ART-treated PLHIV aged 16 to 35 years

Acknowledgments

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Authors

Principal Investigators

Lee Fairlie

Craig Innes

Keren Middelkoop

Kogieleum Naidoo

Michele Tameris

Robert J Wilkinson

Gates Medical Research Institute

Alemnew Dagnew

Lisa Schlehuber

Michael Dunne

Alexander Schmidt