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# Issues in Designing Resilience Trials

Lessons learned from targeting immune resilience with mTOR inhibitors

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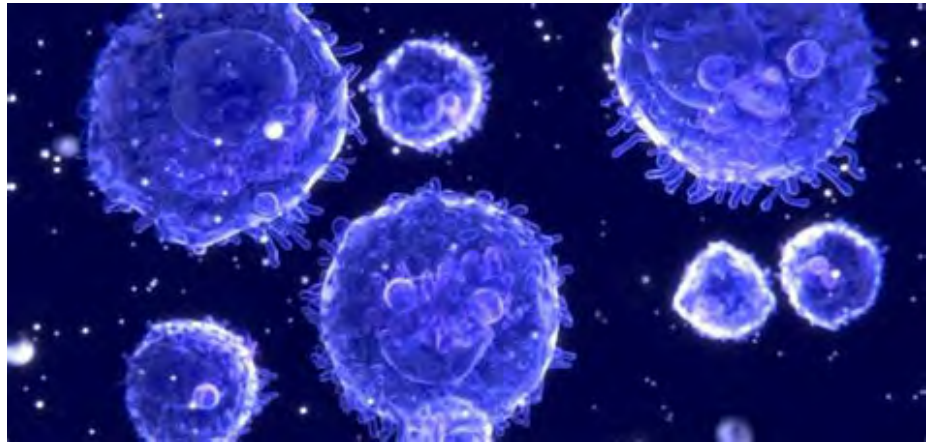
# Disclosure Slide

- Joan Mannick was a shareholder in Novartis and resTORbio who conducted the mTOR inhibitor clinical trials and is currently an employee at Altos Labs. Altos Labs has no connection to and is not responsible for the trials and data being presented.

# Improving immune resilience/function in older adults may have pleiotropic health benefits



Decreased Incidence or Severity of Infections

Improved Vaccination Response

Decreased Cancer Incidence

Decreased Aging Of Other Organ Systems

(Yousefzadeh MJ et al., Nature 2021)

Increased Clearance Of Senescent Cells

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# mTOR inhibitors may improve immune resilience in the elderly as assessed by vaccination response

**Preclinical Study:**

Old Mice

6 weeks
mTOR inhibitor

Improved Influenza
Vaccination Response

\+ ↑ Increased Lifespan

*Chen C et al., Sci Signal, 2009*

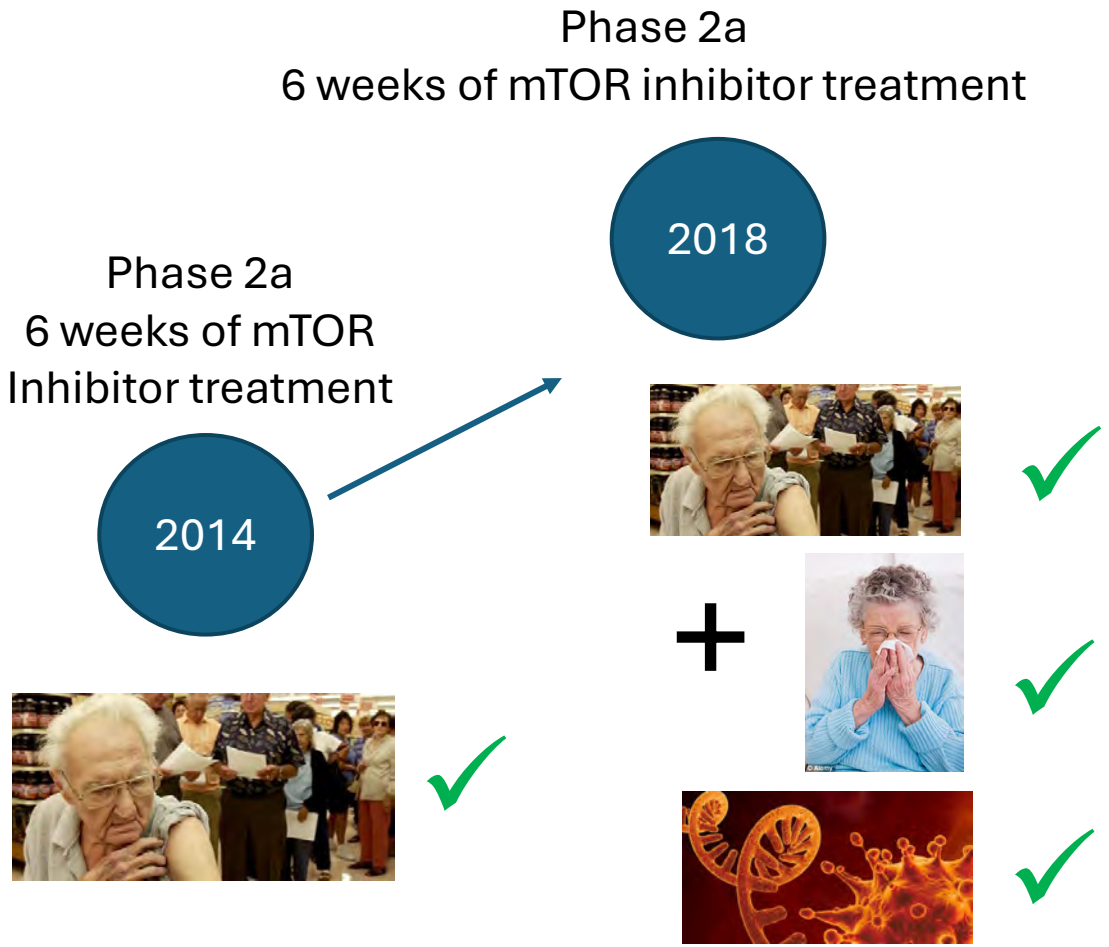
**Novartis Study:**

Elderly Volunteers

6 weeks
mTOR inhibitor

Improved Influenza
Vaccination Response ?

# Phase 2a trials of mTOR inhibitors to flu vaccination response in older adults




Mannick JB et al., Sci Trans Med, 2014
Mannick JB et al., Sci Trans Med, 2018

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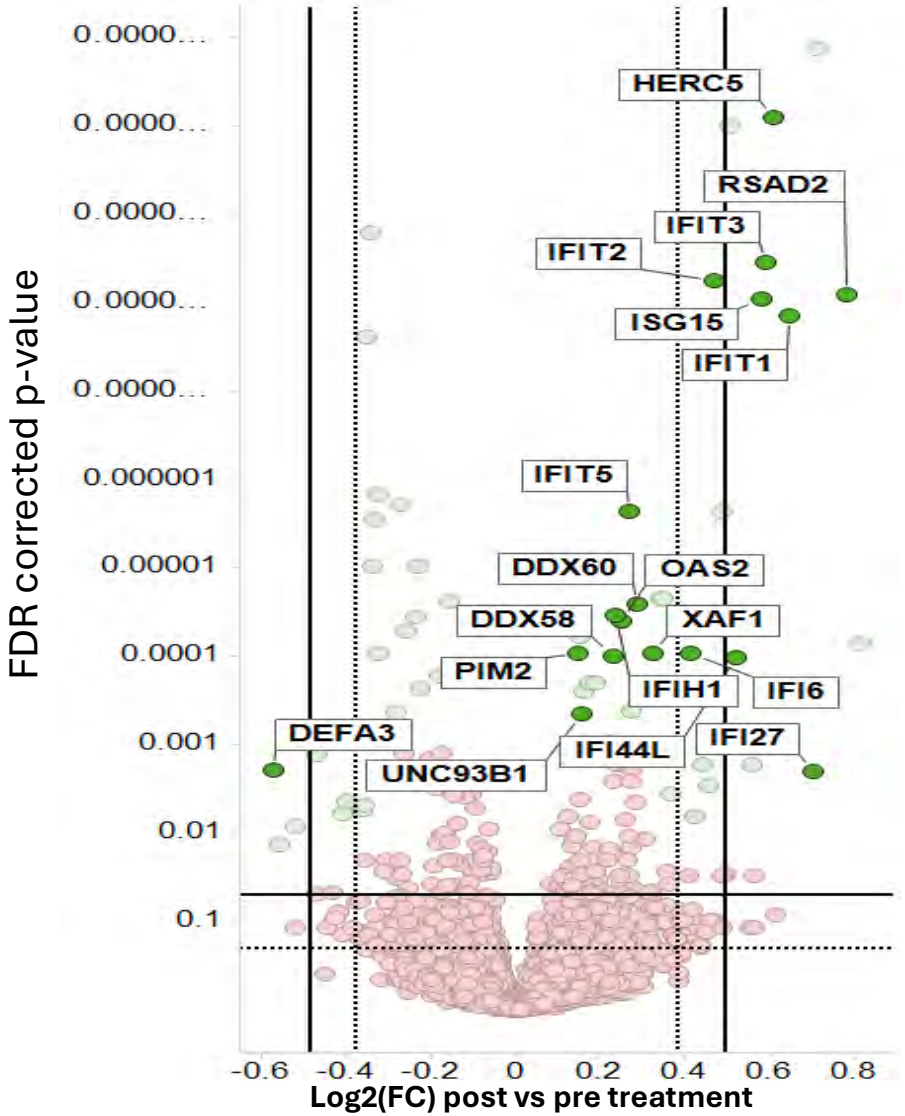
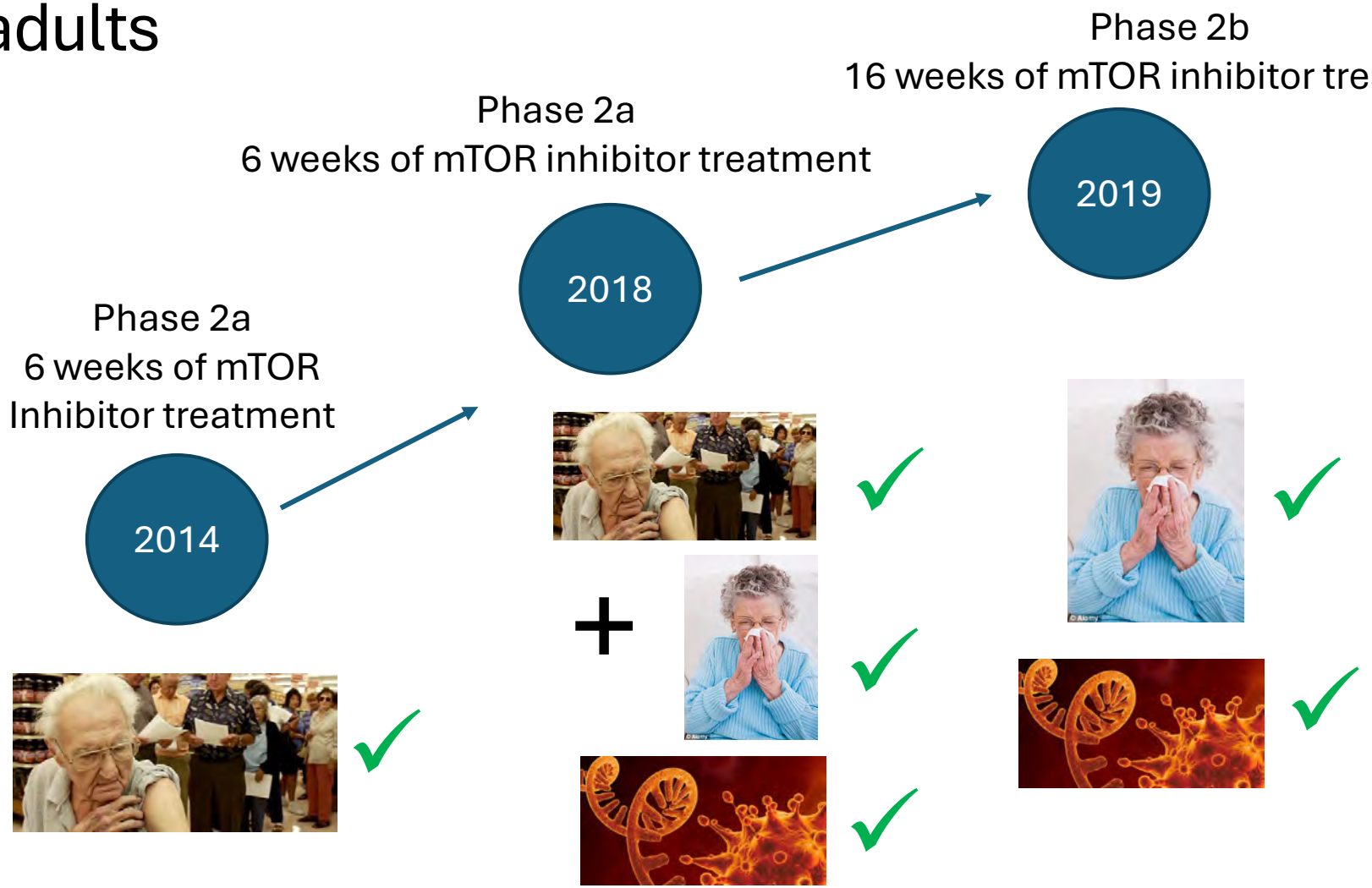
# The main genes upregulated by low doses of mTOR inhibitors are antiviral genes




Mannick et al., Sci Trans Med 2018

# Phase 2b trial of mTOR inhibitors to enhance antiviral immunity in older adults



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# The FDA requested a change in primary endpoint from the Phase 2 to Phase 3 trial

| Trial | Subject Number | Endpoint | |
|---|---|---|---|
| Phase 2b | 652 | Percent of subjects with a **laboratory-confirmed** respiratory tract infection | ✓ |
| Phase 3 | 1052 | Percent of subjects with **symptoms** consistent with a respiratory tract infection | X |

(Mannick JB et al., Lancet Healthy Longevity, 2021)

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# Lessons Learned from the Phase 2 and 3 mTOR Inhibitor Program

1. Targeting immune resiience with low doses or intermittent doses of mTOR inhibitors was well-tolerated in older adults

2. Low doses of mTOR inhibitors consistently and significantly upregulated interferon-induced antiviral responses in older adults

3. Severity rather than incidence of laboratory-confirmed respiratory tract infections may be the appropriate endpoint for clinical trials of mTOR inhibitors

4. mTOR inhibitors may have the greatest benefit in the oldest adult populations (≥ 75 years)

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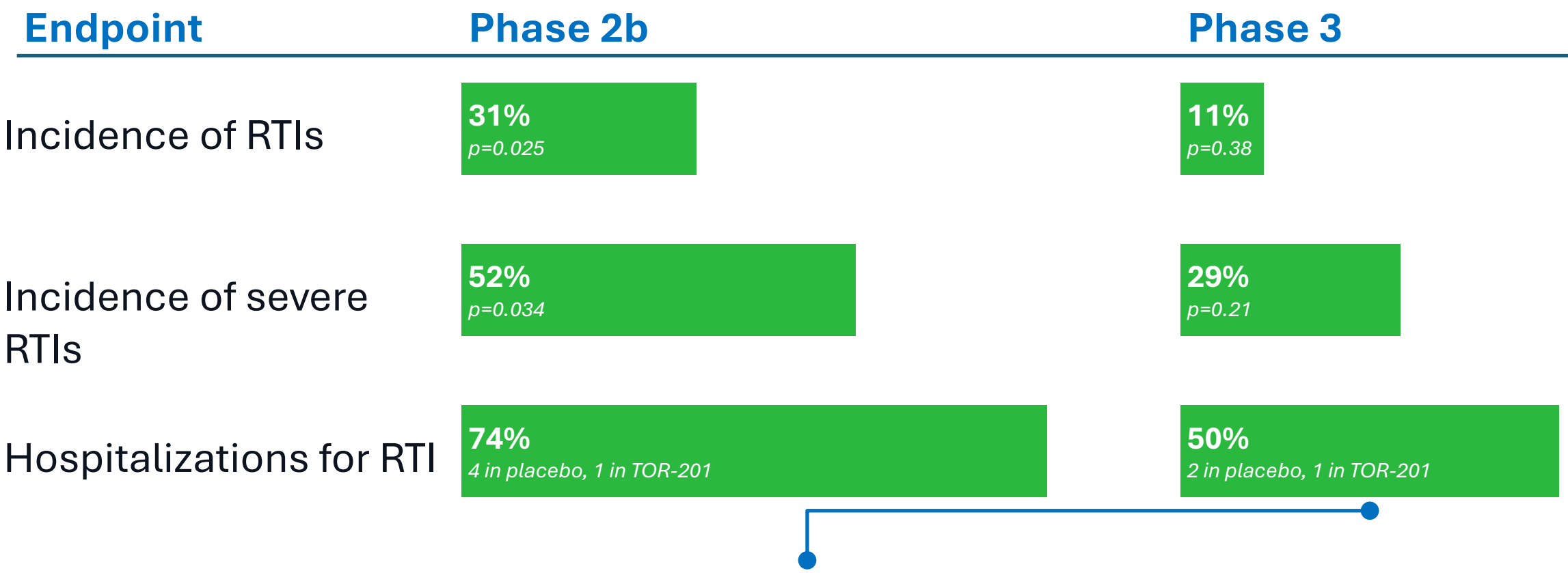
# Lessons Learned: mTOR inhibitors may have greater benefit for reducing the severity than incidence of laboratory-confirmed RTIs

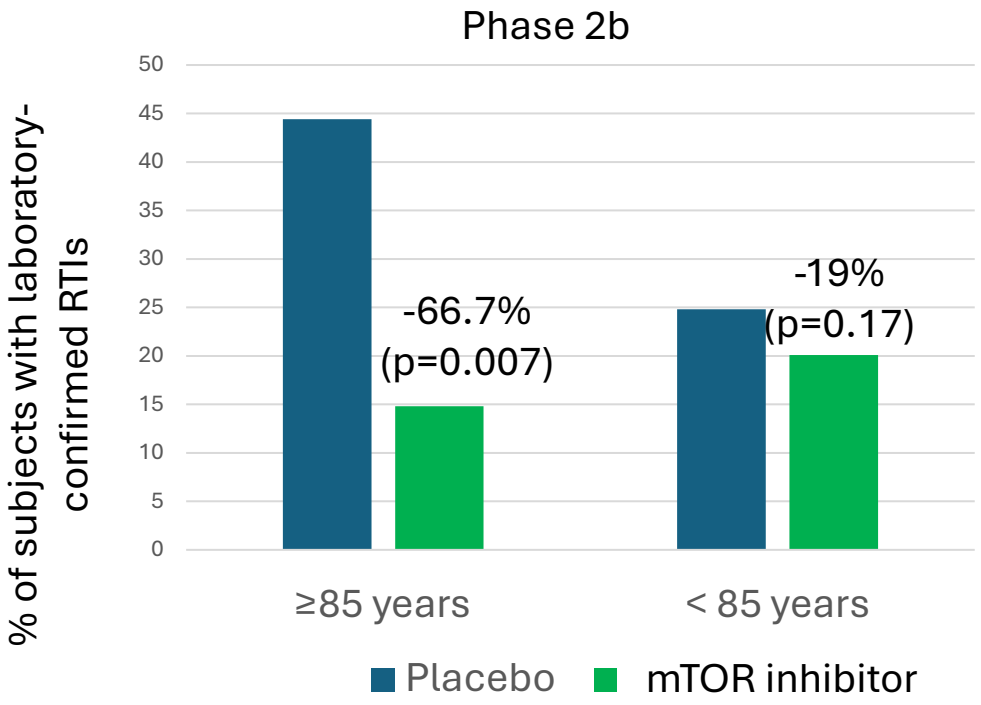
## Percent reduction in key endpoints during mTOR inhibitor clinical trials

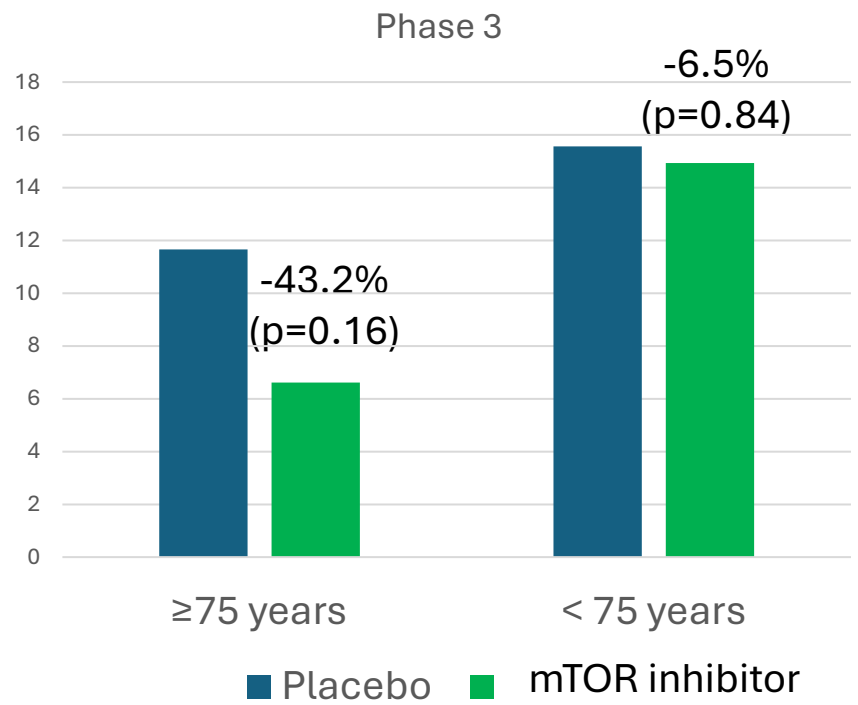



The **Phase 3 trial was underpowered** due to a placebo incidence of laboratory-confirmed RTIs of 14%[1], while it was powered for 28%

(Mannick et al., Lancet Healthy Longevity 2021)

# mTOR inhibition may have greater treatment benefit in people ≥ 75 or 85 years of age




Reduction in RTI incidence was mainly seen in the most elderly populations in the Phase 2b and Phase 3 trial

(Mannick et al., Lancet Healthy Longevity 2021)

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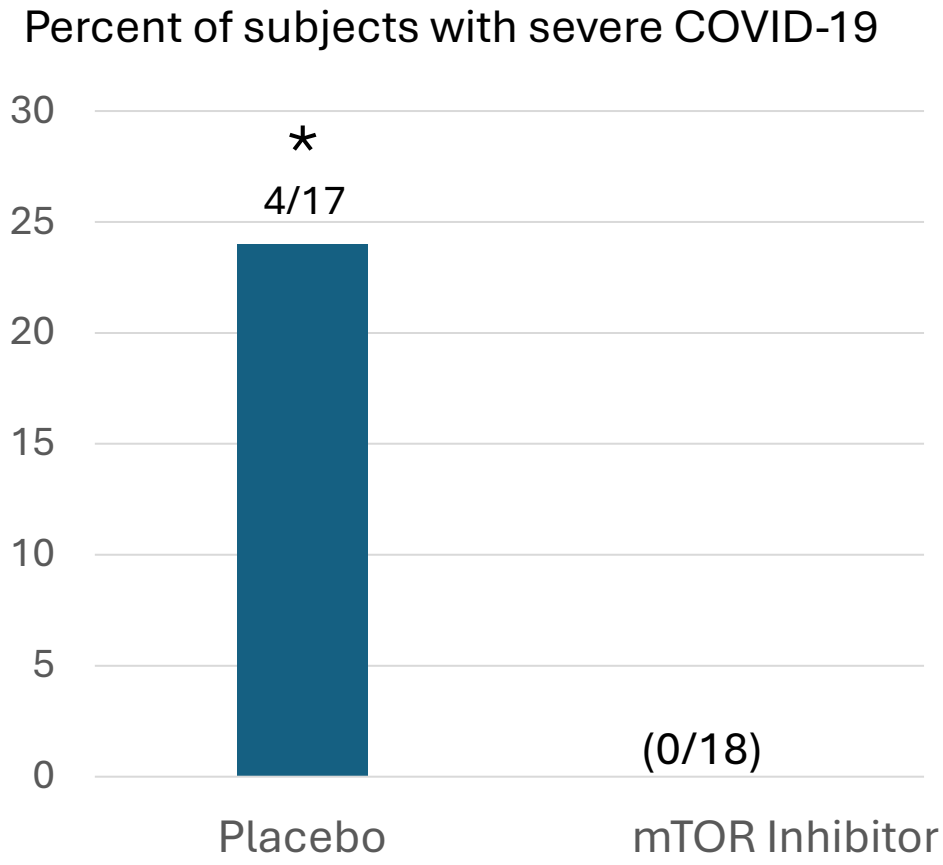
# mTOR inhibition decreased the severity of COVID-19 in nursing home residents

Can low dose mTOR inhibitor therapy decrease the severity of RTIs in a very elderly population?




*= p=0.0455, Chi-Square test

unpublished data

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# Conclusions

- It is likely that we can demonstrate clinically significant improvements in immune resiliency in clinical trials in older adults
  - Incidence or severity of viral respiratory tract infections is a feasible clinical trial endpoint for immune resiliency because RTIs occur frequently in an older adult population and are a large economic burden
- Establishing regulatory precedent for this new area of drug development will be important
- Biomarkers that guide selection of older adult populations with deficient immune responses/resilience will be important for future clinical trials

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# Knowledge Gaps and Research Opportunites

- Knowledge Gaps
  - What biomarkers can be used to identify older adults lacking immune resilience beyond age?
  - What is the regulatory endpoints that FDA will accept for drugs that improve immune resilience?
  - What biologic mechanisms can be targeted to improve immune resilience in older adults beyond mTOR inhibition?
- Research Opportunities
  - Decreasing the incidence or severity of viral respiratory tract infections is a feasible phase 3 endpoint for therapies targeting immune resilience because the event rate is high in older adults
  - Since the immune system may be a fundamental driver of organismal aging, will enhancing immune resilience have more broad benefits on healthspan?