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RTB101 as a Potential Immunotherapy to Reduce the Incidence of Respiratory Tract Infections (RTIs) in Elderly Subjects with Asthma

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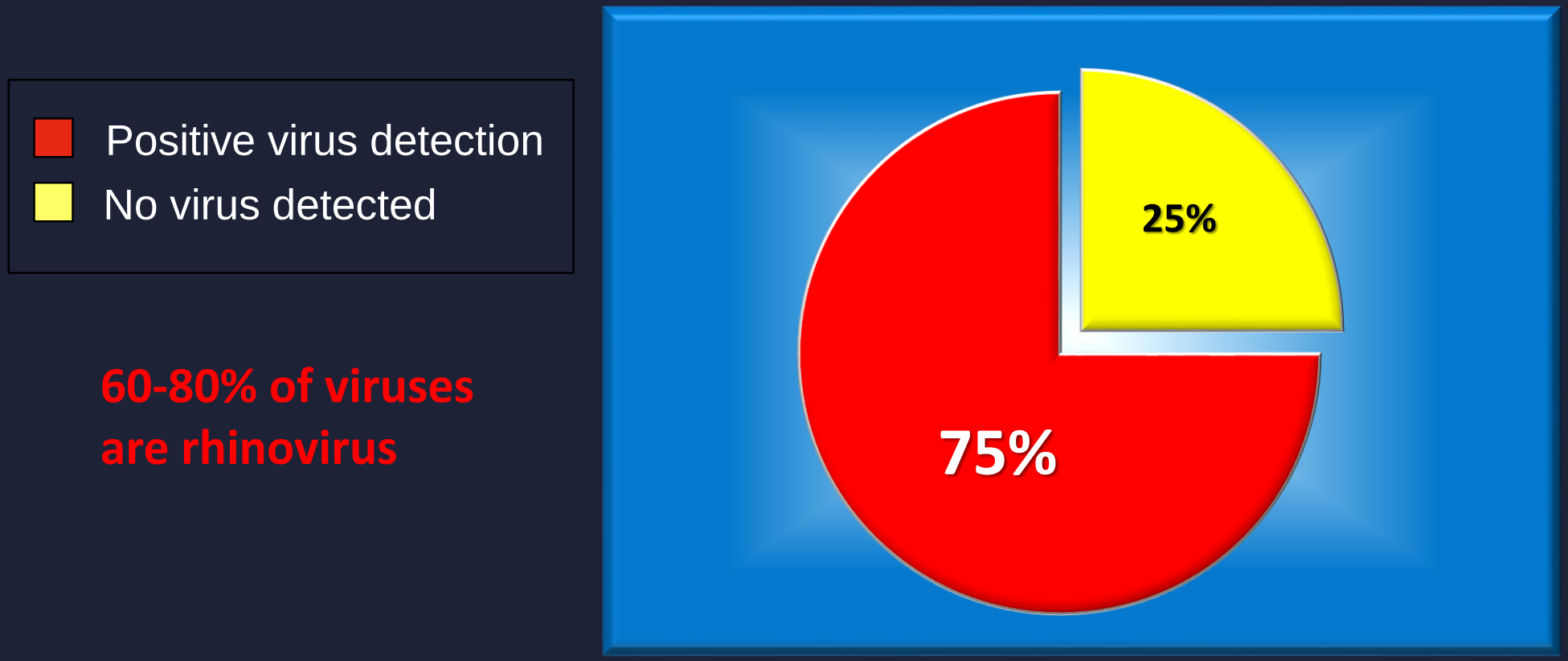
Viral respiratory tract infections are one of the most common causes of asthma exacerbations

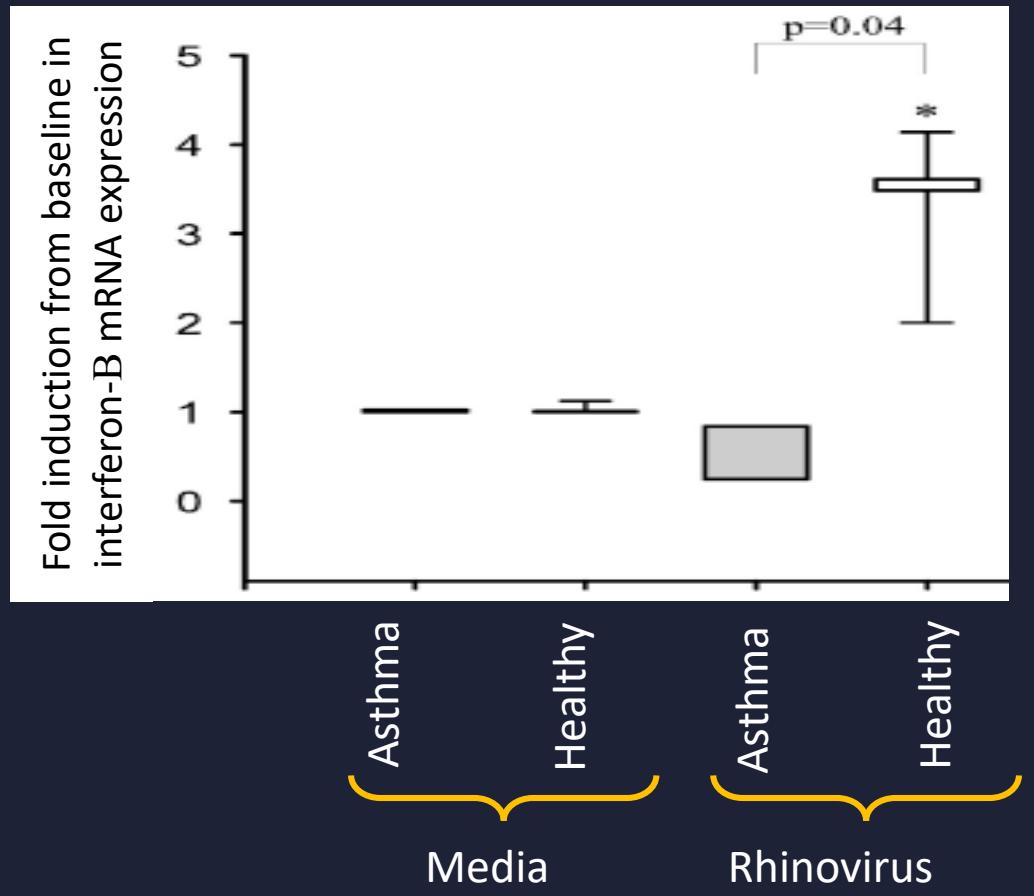
Virus detection in adults with asthma exacerbations



60-80% of viruses are rhinovirus

Antiviral immunity has been shown to be deficient in the airways of some asthmatics

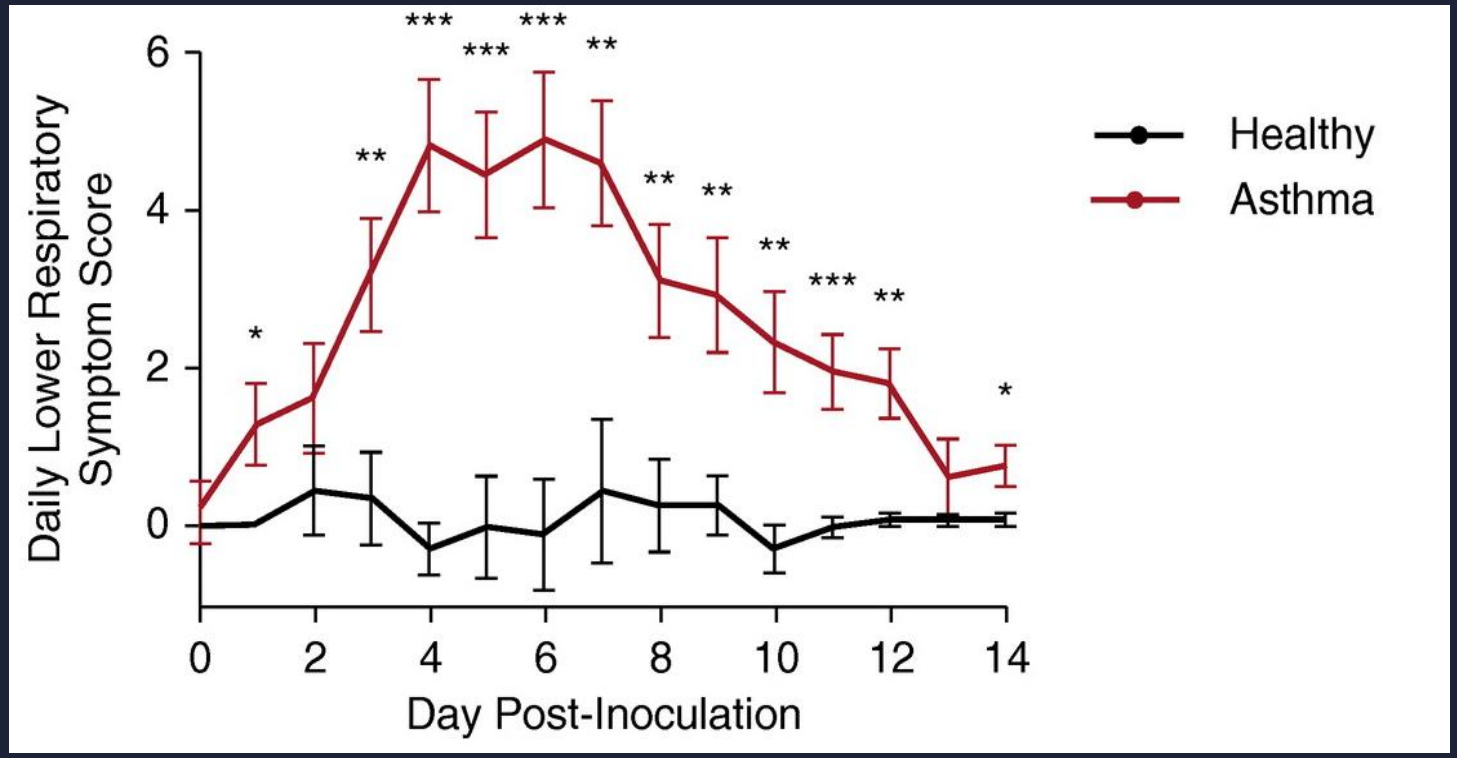
Deficient INF-β expression after rhinovirus infection of primary BECs from asthmatic subjects



Wark et al., *JEM*, 2005; Kelly et al., *J Allergy Clin Immunol*, 2008

Rhinovirus induced lower respiratory illness is worse in asthmatics

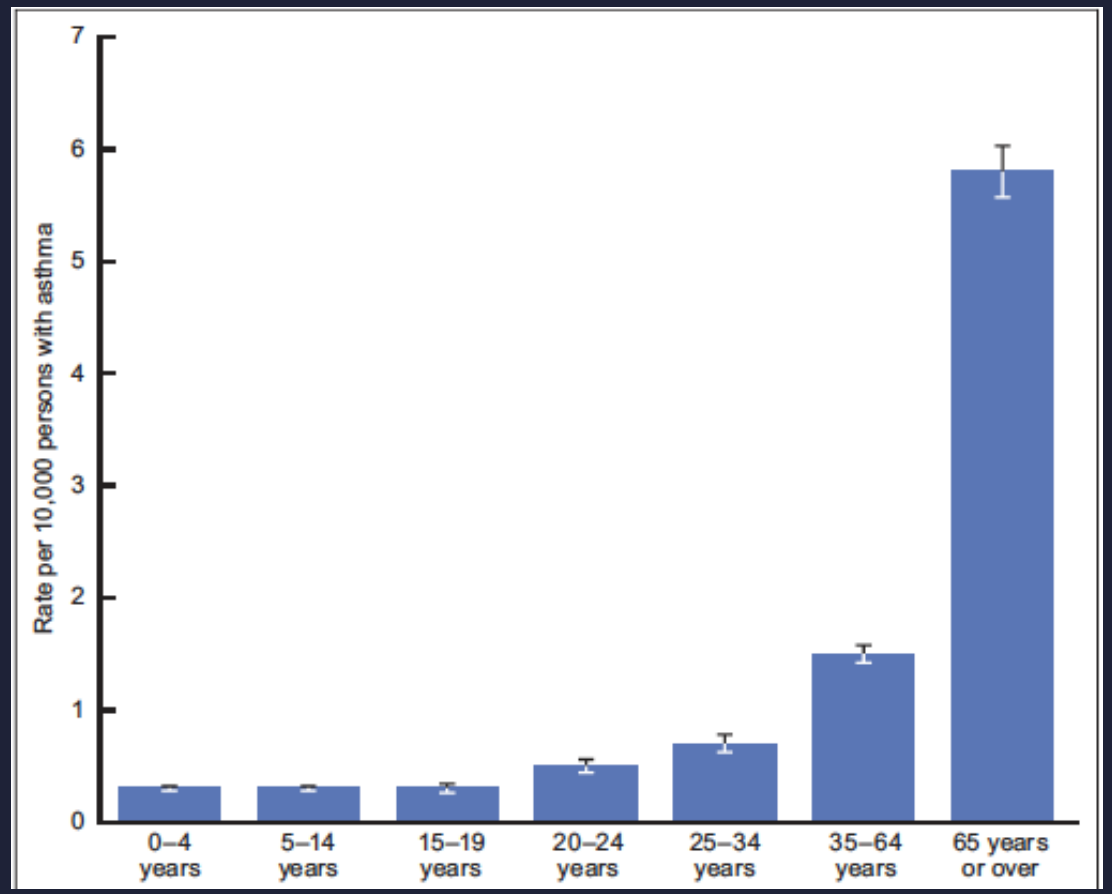
- Adult asthmatics or healthy controls were inoculated with same dose of rhinovirus on day 0
- Lower respiratory symptom scores were significantly higher in asthmatics



Jackson et al., *AJRCCM,* 2014. *p<0.05; **p<0.01; ***p<0.001

Asthma exacerbations are associated with greater morbidity and mortality in older asthmatics

Asthma Death Rates by Age



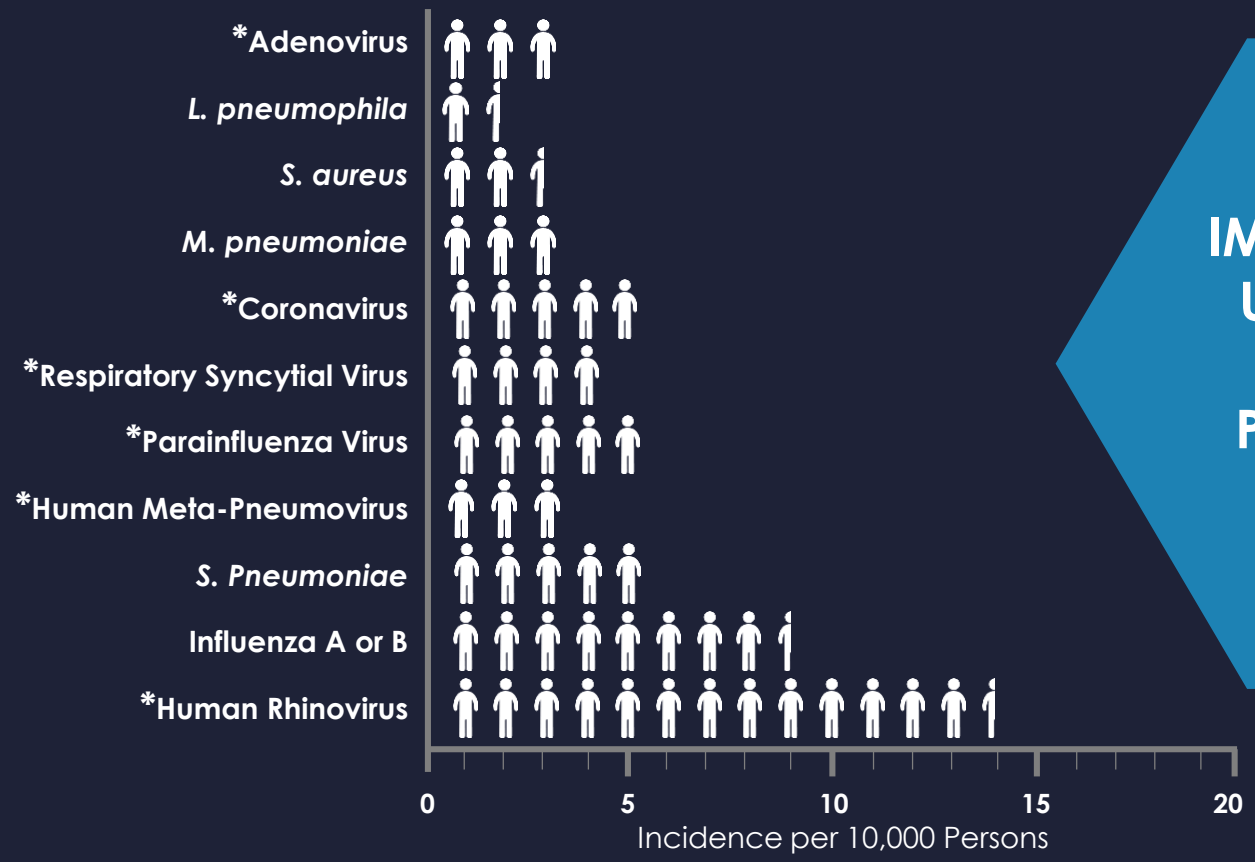
Moorman et al., *National surveillance of asthma*: United States, 2001-2010. Vital Health Stat 3. 2012

Many different viruses cause RTIs most of which lack current therapies

Pathogens detected in elderly subjects hospitalized with community acquired pneumonia

Indicates the annual number of pathogen-specific pneumonia hospitalizations per 10,000 adults ≥ 80

* Viruses with no FDA-approved therapies available

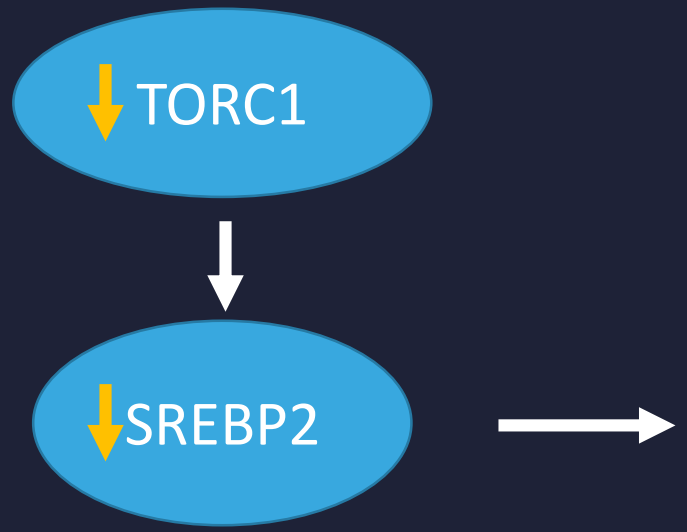


IMMUNOTHERAPY UPREGULATING INNATE PAN-ANTIVIRAL IMMUNITY

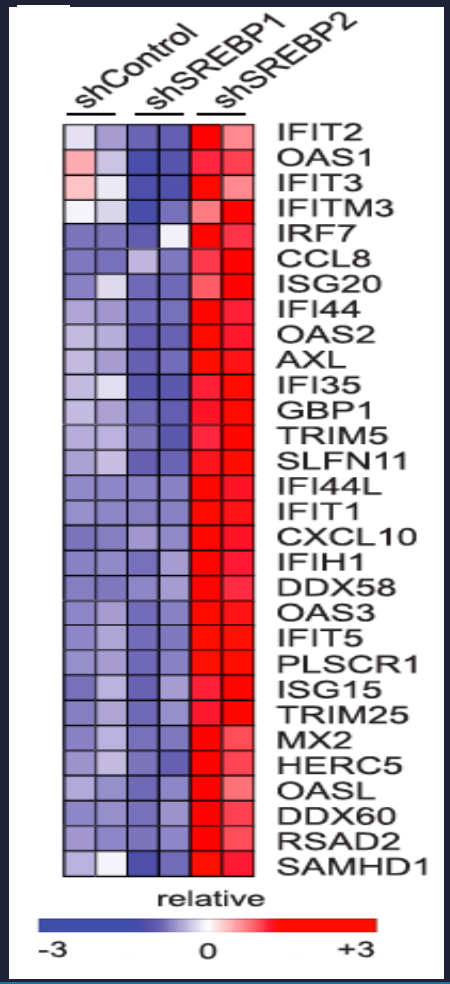
Jain et al., *NEJM,* 2015

TORC1 inhibition may upregulate innate pan-antiviral gene expression and provide protection from multiple different respiratory viruses

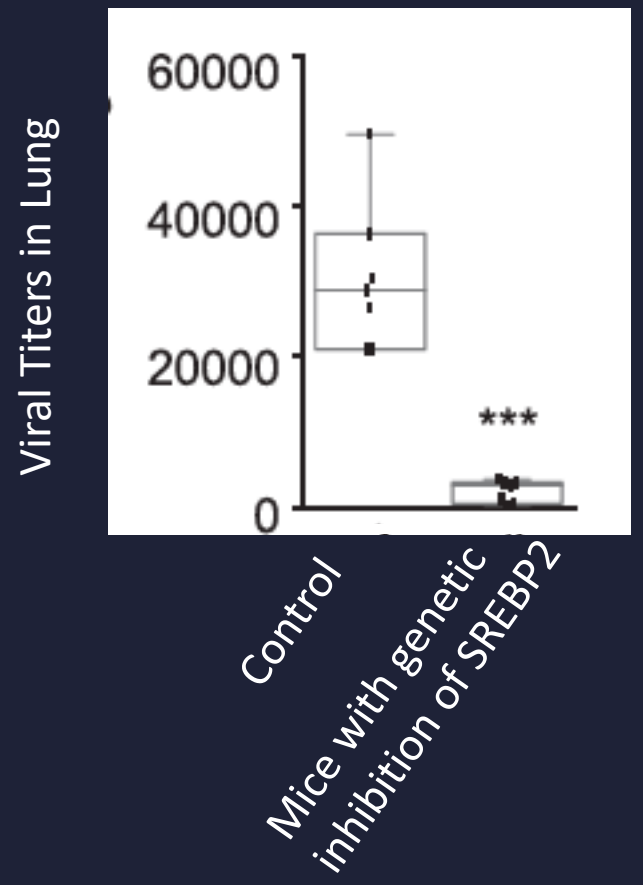
TORC1 Inhibition Leads to Inhibition of SREBP2 Activation



Inhibition of SREBP2 with shRNA Upregulates Antiviral Gene Expression



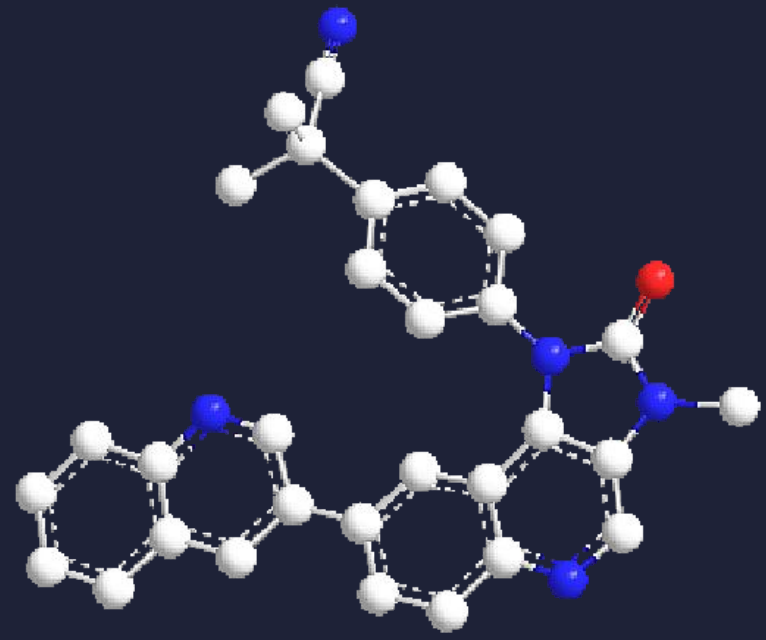
Inhibition of SREBP2 Decreases Viral Titers in Lungs of Mice Infected with a Murine Gammaherpesvirus (MHV-68)



York et al., *Cell*, 2015

RTB101 is an oral, selective and potent inhibitor of TORC1

- Potent oral small molecule TORC1 inhibitor
- Half-life 4-6 hours
- Dose for enhancing antiviral immunity is 1/120th of the maximum tolerated dose in humans
- Dosed in over 1,000 subjects



Phase 2a: TORC1 inhibition was observed to upregulate interferon-induced innate antiviral gene expression pathways in elderly subjects

RNAseq analysis of gene expression in whole blood of elderly subjects treated with TORC1 inhibitors vs placebo

Pathway	Mean FC Genes In Pathway	p-value	Up-regulated Genes
INTERFERON_ALPHA_BETA_SIGNALING	0.08	1e-21.8	**IFI27;IFIT2;IFIT1; IFIT3;MX1;OAS3; ISG15**
INTERFERON_SIGNALING	0.04	1e-36.7	**IFI27;IFIT2;IFIT1; IFIT3;MX1;OAS3; HERC5;ISG15**
CYTOKINE_SIGNALING_IN_IMMUNE_SYSTEM	0.02	1e-43.5	**IFI27;IFIT2;IFIT1; IFIT3;MX1;OAS3; HERC5;ISG15**

The genes whose expression was driving gene pathway upregulation in subjects treated with TORC1 inhibitors were all pan-antiviral genes used by the innate immune system to fight many different respiratory viruses

Mannick et al., *Sci Transl Med*, 2018

In phase 2 clinical trials enrolling > 900 people 65 years of age and older, RTB101 was observed to decrease the incidence of RTIs

Phase 2a trial
264 healthy elderly
RTB101 10 mg QD

42% reduction in the rate of RTIs (p=0.006)

Antiviral defense systems were upregulated in blood

RTB101 was well-tolerated

Phase 2b trial
652 high-risk elderly
RTB101 10 mg QD

30.6% reduction in the percent of patients with laboratory-confirmed respiratory tract infections (p=0.025)

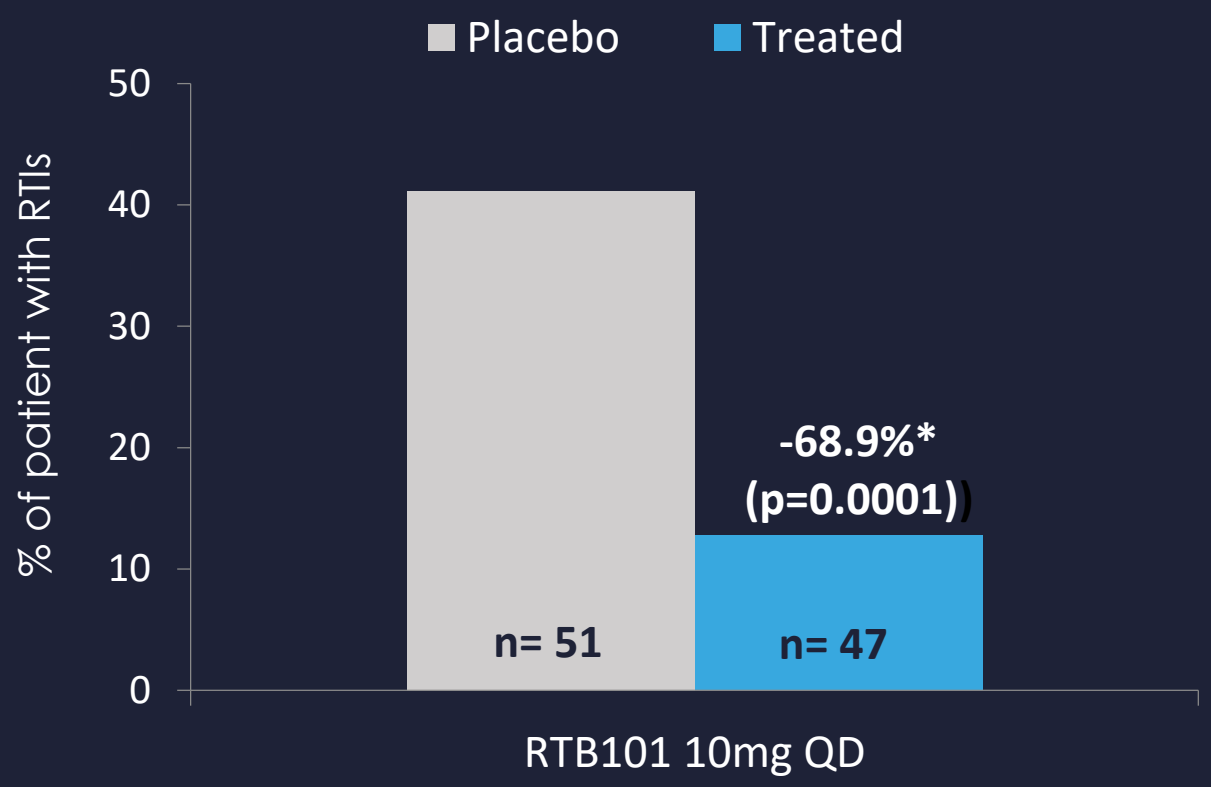
52.1% reduction in percentage of subjects with severe laboratory-confirmed respiratory tract infection symptoms (p=0.034)

RTB101 was well-tolerated

QD = once daily

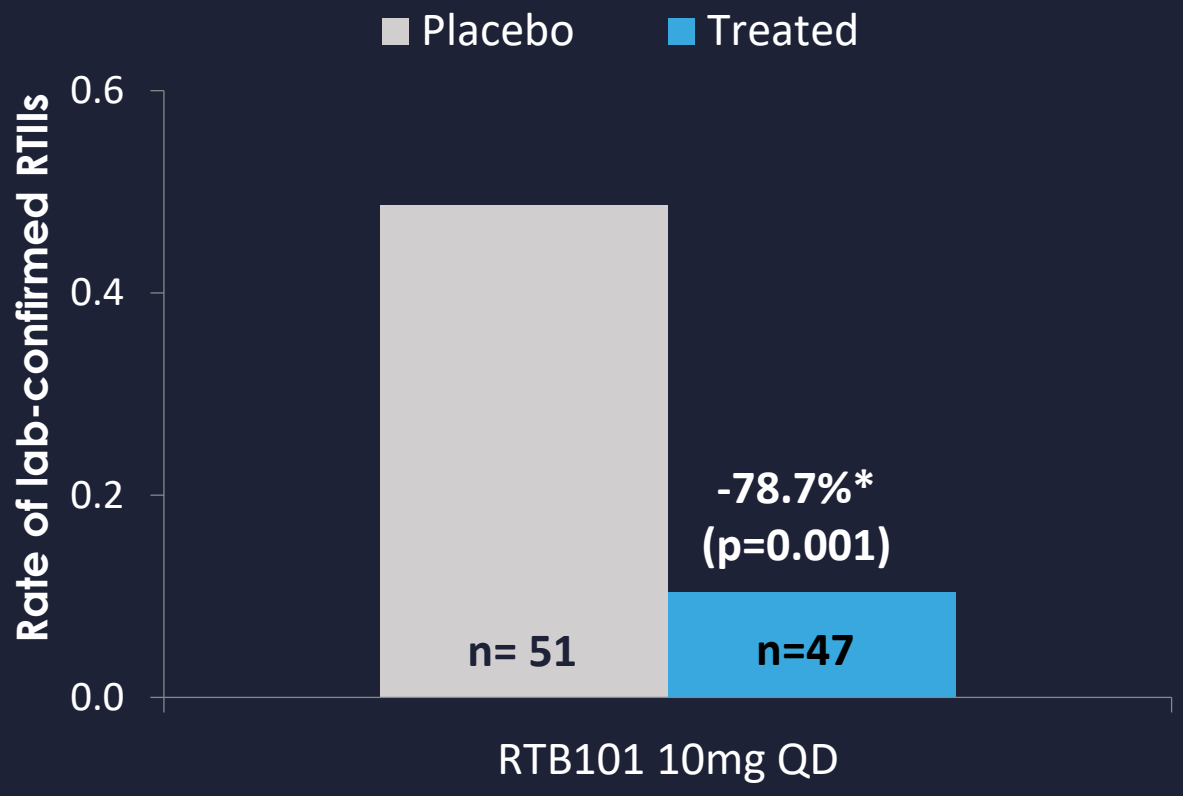
RTB101 10 mg once daily was observed to decrease the incidence of laboratory-confirmed RTIs in asthmatics

Percentage of asthmatics who developed lab-confirmed RTIs



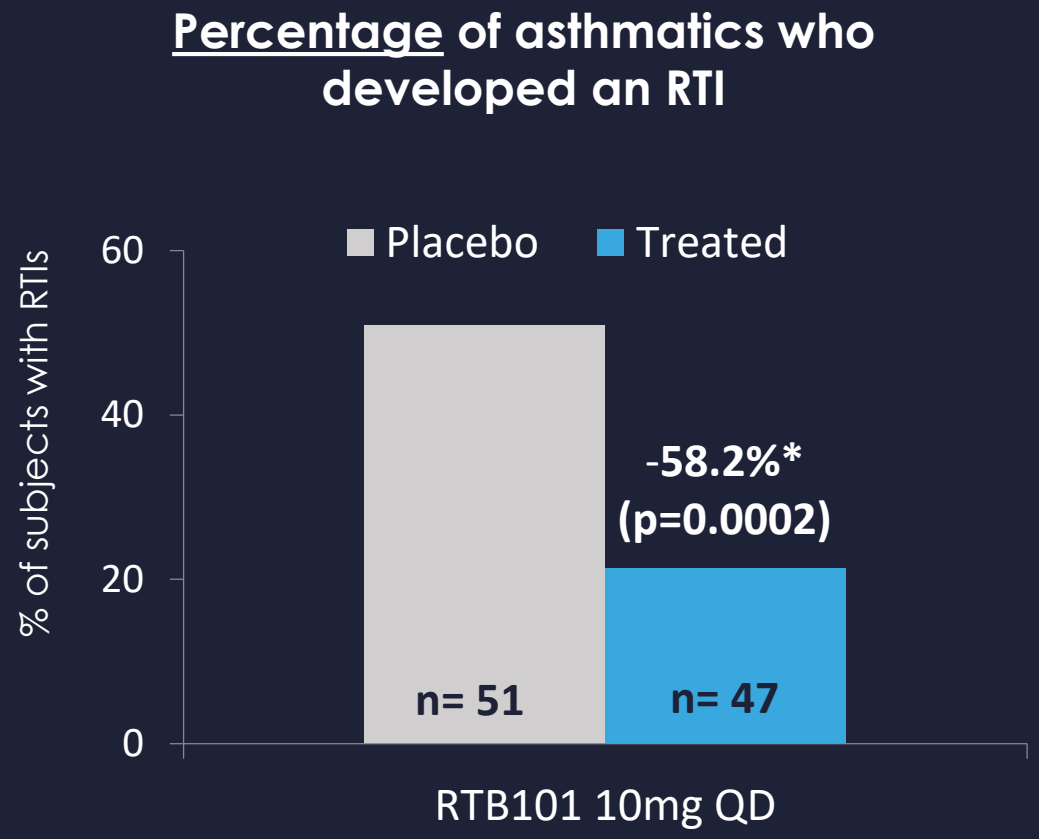
* Odds Ratio=0.105 (CI=0.038-0.290)

Rate of lab-confirmed RTIs in asthmatics

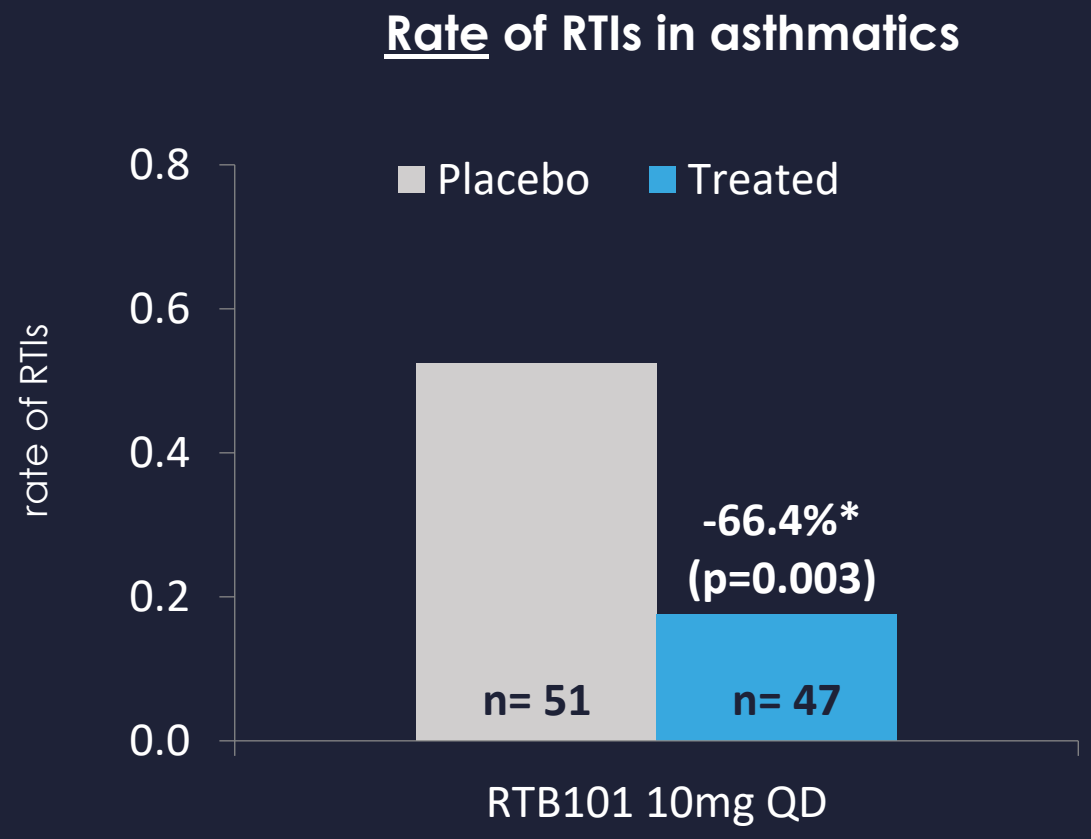


) *Odds Ratio=0.213 (CI=0.093-0.486)

RTB101 10mg once daily was observed to decrease the incidence of all RTIs (laboratory-confirmed and non-laboratory confirmed)

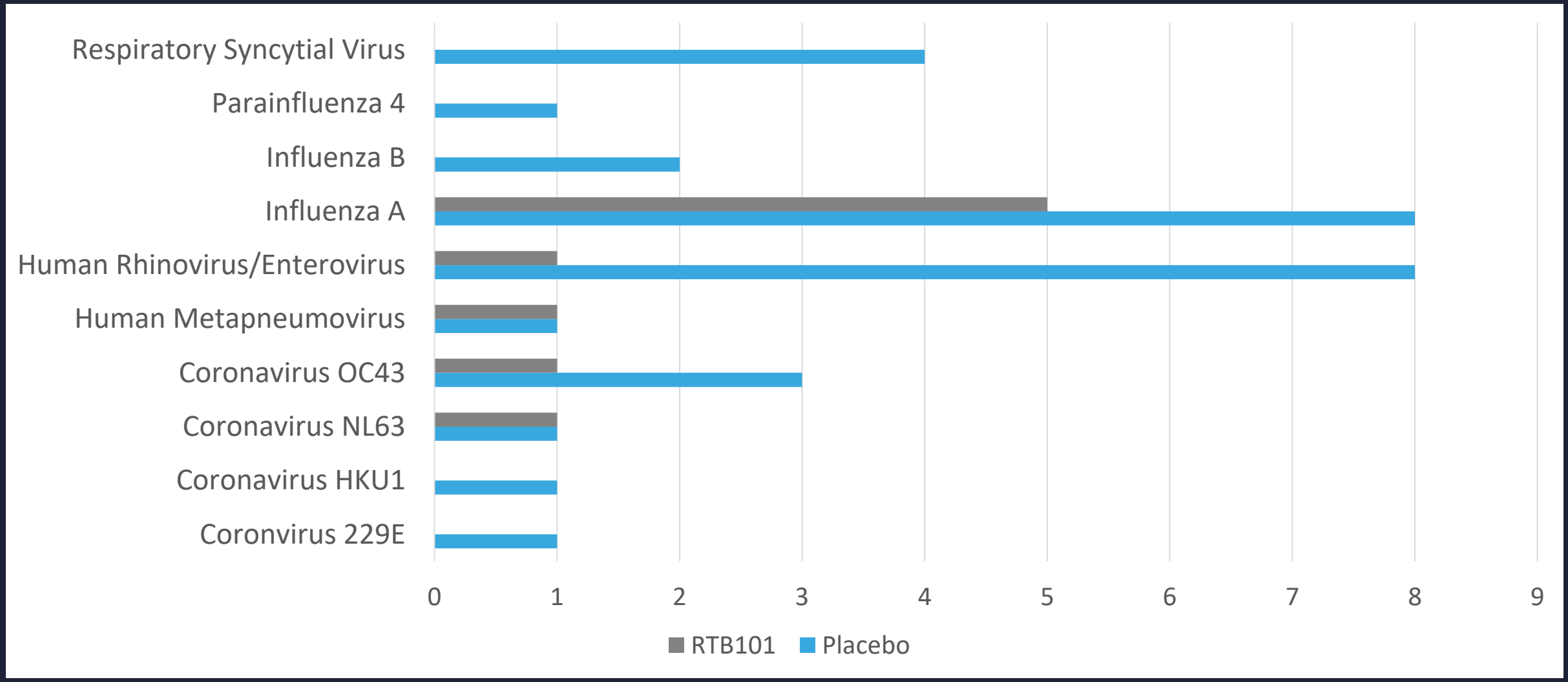


*Odds Ratio=0.144 (90% CI 0.059-0.351)



*Odds Ratio=0.336 (CI 0.175-0.645)

RTB101 10mg once daily was observed to decrease the incidence of RTIs caused by multiple viruses including rhinovirus



RTB101 was well-tolerated when given to elderly subjects for 16 weeks during winter cold and flu season

Adverse Events (AEs) and serious AEs reported during the 16-week period by subjects receiving RTB101 10mg QD or placebo:

- Adverse events were comparable between the RTB101 10 mg QD and placebo cohorts

	% of patients in treatment group	
	RTB101 10mg QD	Placebo
Mild AEs	74.4%	71.7%
Moderate AEs	38.1%	40.6%
Severe AEs	5.7%	7.8%
Serious AEs	4.5%	7.8%
Discontinued study drug due to an AE	5.1%	5.6%

Adverse Events (treatment emergent, non-RTI)
occurring in ≥2% of patients in 10 mg or placebo cohorts through week 16

Preferred Term	RTB101 10 mg QD (N=176) n (%)	Placebo (N=180) n (%)
Headache	10 (5.7)	13 (7.2)
Constipation	3 (1.7)	10 (5.6)
Diarrhea	8 (4.5)	6 (3.3)
Fatigue	6 (3.4)	6 (3.3)
Fall	6 (3.4)	6 (3.3)
Nausea	1 (0.6)	6 (3.3)
Anemia	2 (1.1)	5 (2.8)
Arthralgia	2 (1.1)	5 (2.8)
Blood creatinine increased	4 (2.3)	4 (2.2)
Hypertension	4 (2.3)	3 (1.7)
Pain	2 (1.1)	4 (2.2)
Back Pain	4 (2.3)	2 (1.1)
Hyperglycemia	4 (2.3)	2 (1.1)
Limb injury	1 (0.6)	4 (2.2)
Tooth abscess	4 (2.3)	1 (0.6)
Decreased appetite	1 (0.6)	4 (2.2)
Skin abrasion	4 (2.3)	0

RTB101 10mg once daily was observed to decrease the incidence of RTIs caused by multiple viruses in older asthmatics

- In two phase 2 studies enrolling > 900 elderly subjects, RTB101 10 mg QD was observed:
  - To be well-tolerated
  - To reduce the incidence of RTIs
- A pre-specified analysis indicated that RTB101 10 mg once daily may be of particular benefit in asthmatics age 65 years and older:
  - 68.9% reduction in the percentage of asthmatics who developed one or more laboratory-confirmed RTIs
  - 58.2% reduction in the percentage of asthmatics who developed a RTI of any kind (both laboratory-confirmed and not laboratory-confirmed)
  - Reduction in the incidence of RTIs caused by multiple viruses

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