Safety and Efficacy Results from Phase 1 and Phase 2a Trials Using an Anti-Type A and B Influenza Immunotherapeutic that is Also Synergistic with Oseltamivir in Mice

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Target Status and Product Profile

Status:
Breakthrough Therapy and Fast Track Designations granted by the FDA in April 2023

Potential indications: Treatment, pre- and post-exposure prophylaxis in high-risk influenza patients

- Adults 65 years of age and older
- Immunocompromised due to a disease or medications (autoimmune, cancer, etc.)
- Patients with respiratory, cardiovascular, kidney, metabolic, neurological disorders

- Pre- and post-exposure prophylaxis of high-risk patients and critical services personnel
  - High-risk patients in nursing homes/assisted living
  - Hospitalized
  - First responders/military/medical providers
  - Critical infrastructure operators

- Administration Routes
  - Intravenous
  - Subcutaneous and Intramuscular administration in development

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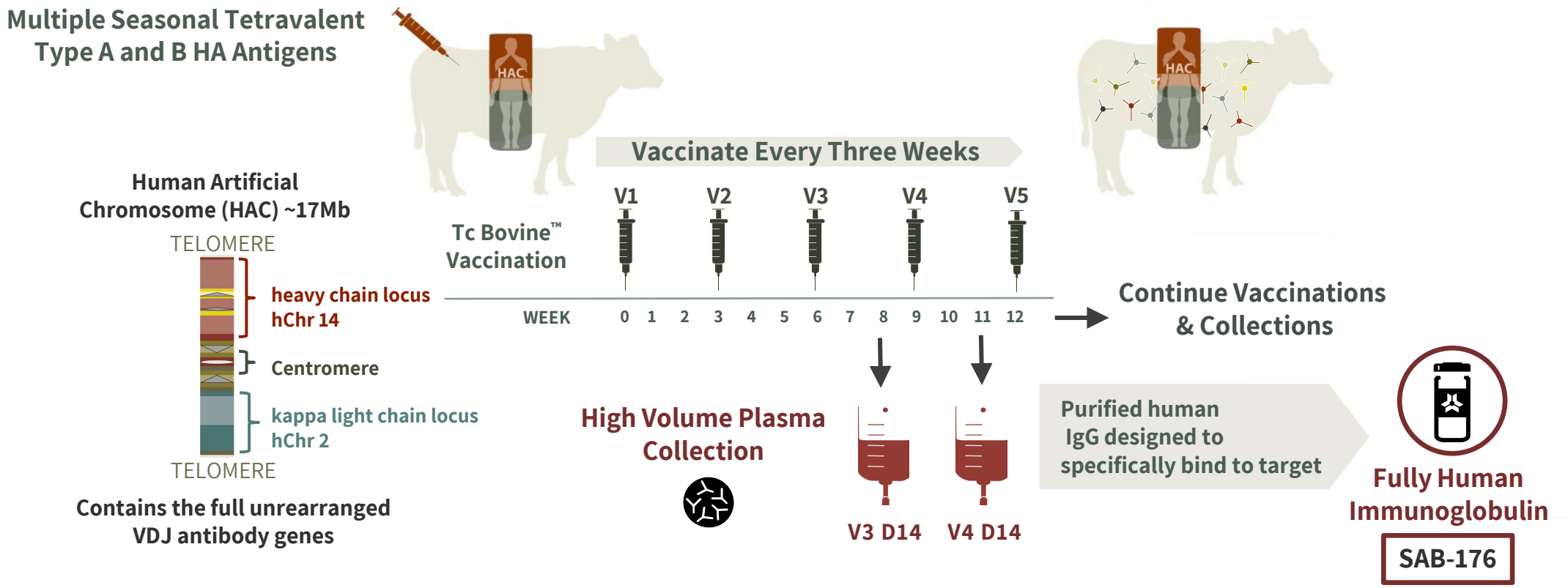
DiversitAb™ Development Process for SAB-176



SAB-176 Demonstrates Higher Titers vs Anti-Flu Human IVIG

SAB-176 exceeds potency titers by up to 64x compared to anti-flu human IVIG, previously utilized in Ph2 clinical studies, across a panel of 14 influenza strains (Seasonal and Pandemic)

		H1N1					H3N2				B-Vic			B Yam	
	Sample Started at 5mg/ml	A/California/4/2009 (Pandemic Strain)	A/Michigan/45/2015	A/Brisbane/02/2018	A/Guangdongmaonan/2019	A/Victoria/2570/19	A/Singapore/INIFMH-16-0019/2016	A/Kansas/14/2017	A/Hong Kong/45/2019	A/Cambodia/e0826360	B/Maryland/15/2016	B/Colorado/06/2017	B/Washington/02/2019	B/Phuket/3073/2013	B/California/12/2015
SAB-176	**SAB-176**	**512 (8-16X)**	**512 (16X)**	**512 (16-32X)**	**512 (16-32X)**	**256 (16-32X)**	**512 (8-32X)**	**256 (8-64X)**	**256 (16-32X)**	**256 (16-32X)**	**256 (16-32X)**	**256 (16-32X)**	**128 (16-32X)**	**128 (16X)**	**128 (16-32X)**
Human Anti-Flu IVIG	2018	64	32	32	32	8	64	32	16	16	16	16	8	8	8
	2017	32	32	16	16	16	64	32	16	32	16	16	8	8	8
	2013	32	32	32	16	16	16	4	8	32	8	8	4	8	4
Negative Control Antibody		<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1	<1

Seasonal Flu Strain Year: **18-19** **19-20** **20-21** **18-19, 19-20, 20-21**

HUBER LAB, USD, MAR 2021

Values indicate HAI titer. Numbers in parenthesis indicate the titer ratio of SAB-176 to hIVIG

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Phase 1: Safety, Tolerability, and Pharmacokinetics Study of SAB-176 in Healthy Adults

Study design: Randomized, Double-Blind, Placebo-Controlled, Single Ascending Dose

Cohort	Number of Subjects Receiving SAB-176				Number of Subjects Receiving Saline Control
	1 mg/kg	10 mg/kg	25 mg/kg	50 mg/kg	
1	2				1
2		4			2
3			6		2
4				8	2

Results:

- SAB-176 was safe and well tolerated by the healthy subjects.
- No clinically meaningful changes from baseline were observed.
- The most commonly reported TEAE was headache (2 subjects [10.0%] in SAB-176 and 1 subject [14.3%] in the placebo treated groups).
- T ½ ranged from 3 to 4 weeks for various strains.

Safety, Tolerability, and Pharmacokinetics of SAB-176 in Healthy Participants - Full Text View - ClinicalTrials.gov

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Phase 2A: Trial Design

- **Study design: Randomized, Double-Blind, Placebo-Controlled Influenza Challenge Study**
- **Study sample size**: 62 Healthy volunteers (18-45 years of age)
  - 30 subjects were randomized to SAB-176 and 30 were randomized to placebo (normal saline).
- **Study flow:**
  - Participants were admitted to the hVIVO facility 2 days prior to inoculation and were quarantined for up to 11 days (Day -2 to 8) with Influenza challenge occurring on day 0 and SAB-176/placebo infusion on day 1. Participants were discharged on day 8. Participants returned for 1 outpatient visit on day 28.
- **Challenge virus**: A pandemic H1N1 A/California/2009-like challenge virus was produced by Meridian Life Sciences under Good Manufacturing Practices (Watson et al., 2015; Leibowitz et al., 2020)
- **Investigational treatment:** Subjects were treated with a single IV infusion of 25 mg/kg of SAB-176 or received placebo 20-24 hours after influenza challenge.
- **Assessment:** Subjects were continuously monitored with nasal pharyngeal viral swabs and other samples collected twice daily for 8 days.

EudraCT # 2021-001254-56
ClinicalTrials.gov number NCT04850898

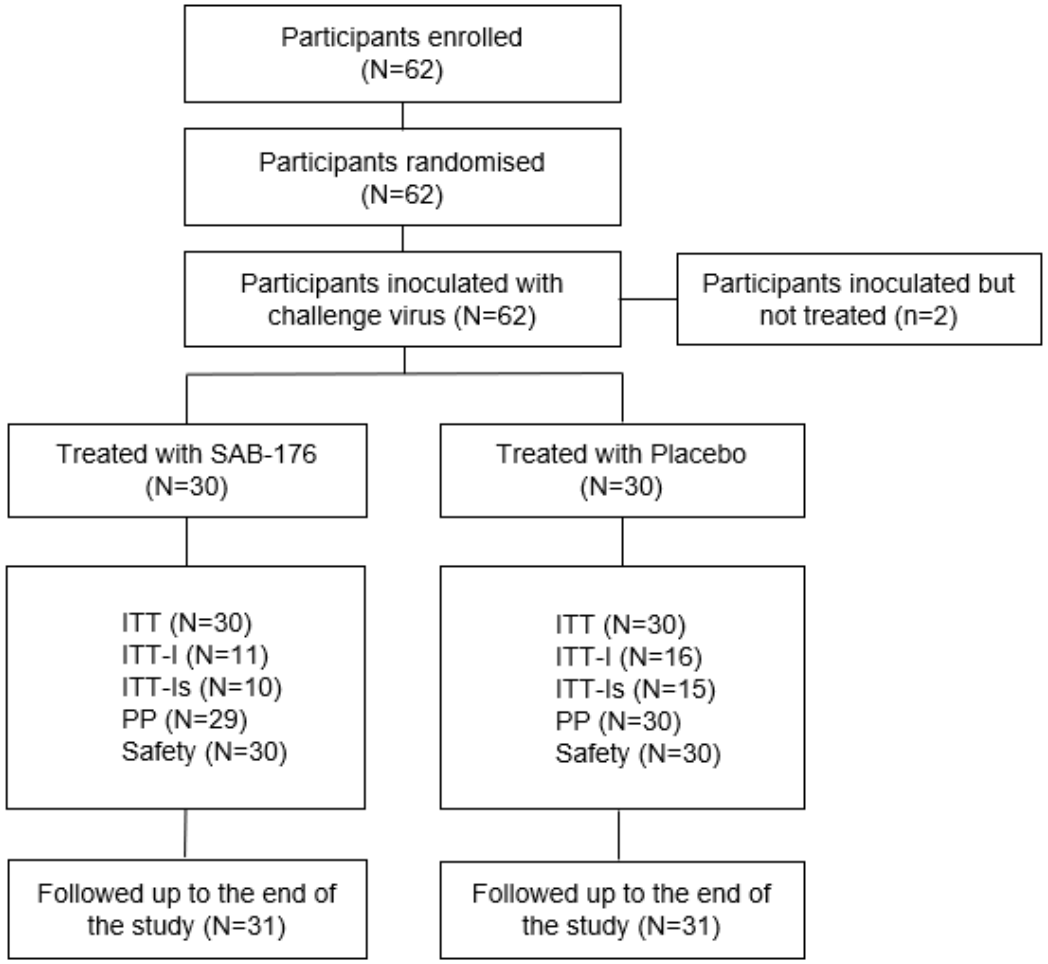
Phase 2A: Trial Design, cont.

Primary Outcome Measure:

- Area under the viral load-time curve (VL-AUC) of Influenza A/California/2009 H1N1 virus as determined by qRT-PCR on nasal samples of SAB-176 when compared to placebo. [Time Frame: 8 Days]

Secondary Outcome Measures:

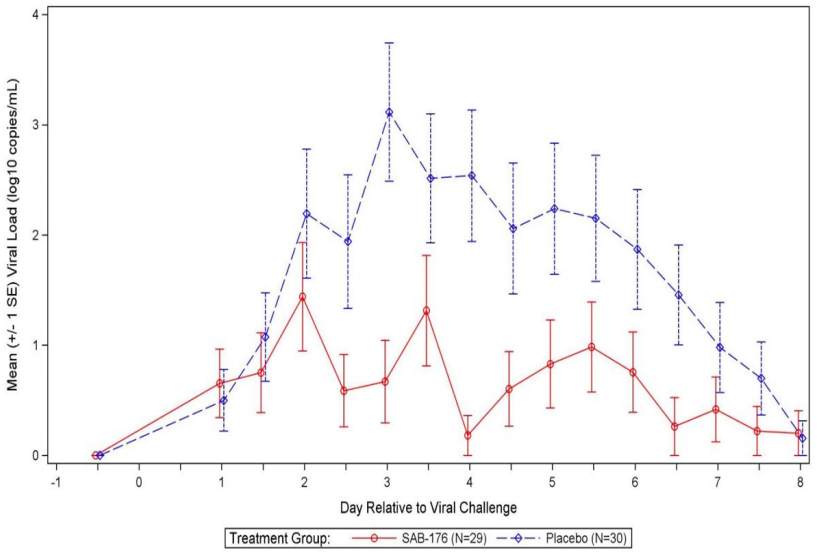
- Area under the curve over time of total clinical symptoms score (TSS-AUC) as measured by graded symptom scoring system to evaluate the effect of SAB-176 in reducing symptoms as compared to placebo. [Time Frame: 8 Days]
- Duration of influenza quantifiable by cell culture measurement to evaluate the effect of SAB-176 in reducing viral loads in cell culture as compared to placebo.



Phase 2A Results: Established Proof-of-Concept for SAB-176 Met Primary Endpoint of Viral Load Reduction in Phase 2a Challenge Study

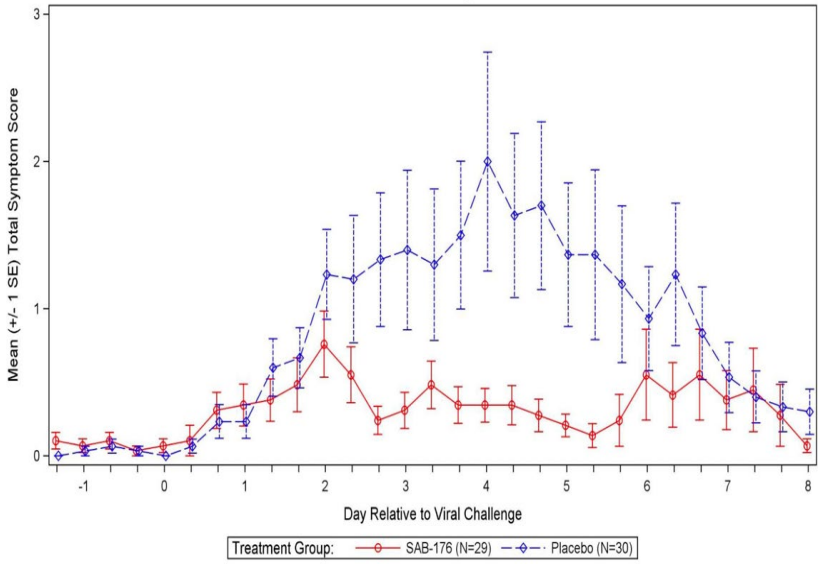
Achieved Statistically Significant (p = 0.026) Reduction in Viral Load

Mean Viral Load by Nasal Samples qRT-qPCR by Day Relative to Viral Challenge



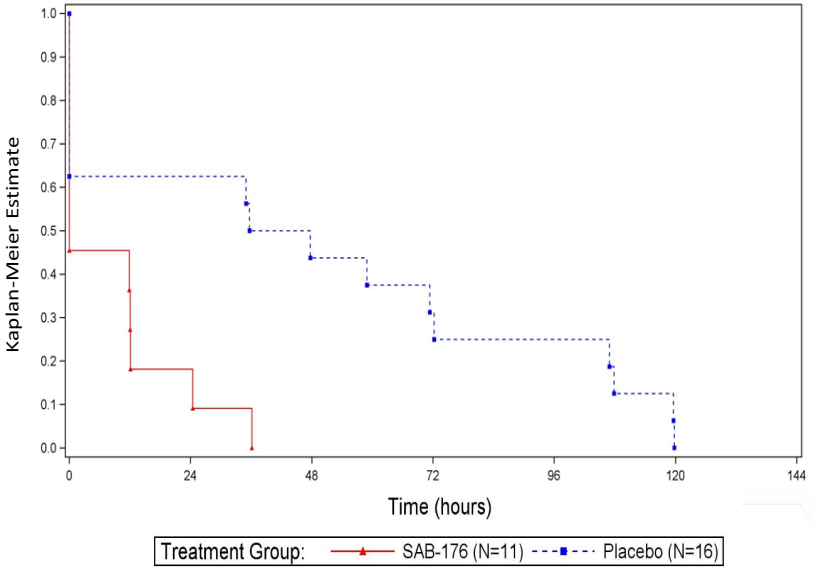
SAB-176 Achieved Statistically Significant (p = 0.013) Improvement in Symptoms at Day 4

Mean Total Symptom Score by Day Relative to Viral Challenge



SAB-176 Shortened Time of Viral Shedding as Measured by Lack of Culturable Virus

Time to Resolution of Positive Viral Cultures Following First Positive Culture Starting 2 Days After Intranasal Viral Challenge



SAB-176 not specifically targeted to pH1N1 strain used in challenge study

Statistically significant reduction in virus load confirms high cross reactivity to pandemic strain (not targeted with immunogen)

Reinforces ability to generate broadly neutralizing antibodies to viral variants

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Combination Treatment of SAB-176 with Oseltamivir in H1N1 Challenged Mice

- Oseltamivir is the most commonly used neuraminidase inhibitor to treat influenza and provides only modest benefit when used to treat severe influenza.
- A significant limitation of oseltamivir is that anti-viral resistant influenza strains commonly arise and negate or reduce its effectiveness.
- This highlights the critical need to discover counter measures that can be used alone or in conjunction with oseltamivir and other neuraminidase inhibitors
- NIAID/DMID sponsored studies to investigate the effect of SAB-176 or precursors
    - A study in mice using a resistant Oseltamivir pH1N1 challenge strain
    - A combinatorial therapeutic approach in mice using a non-resistant Oseltamivir pH1N1 challenge strain.

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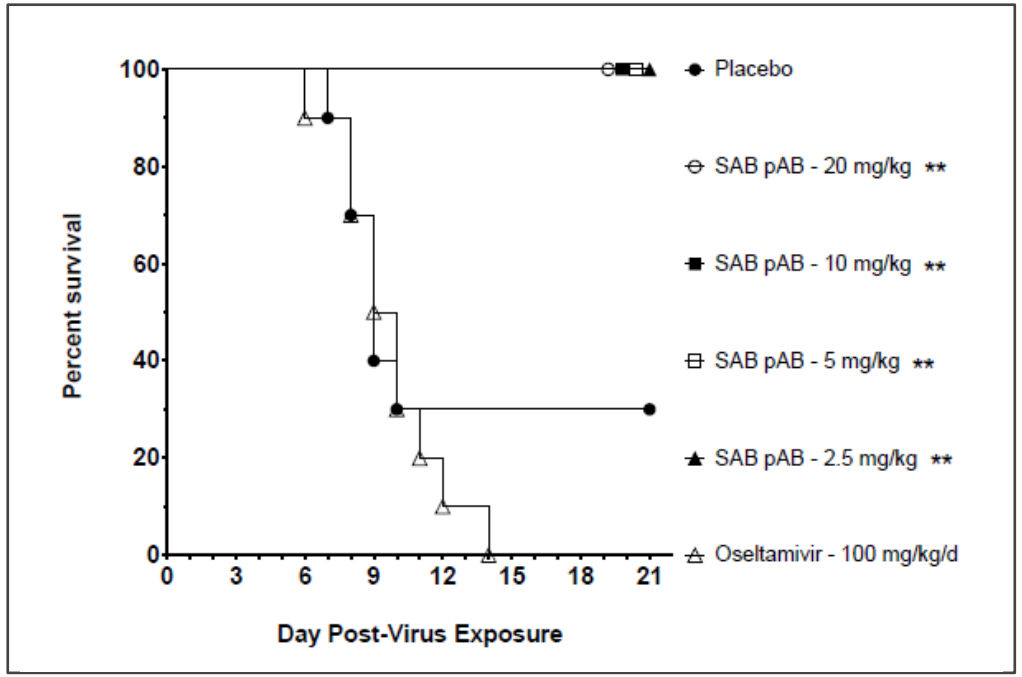
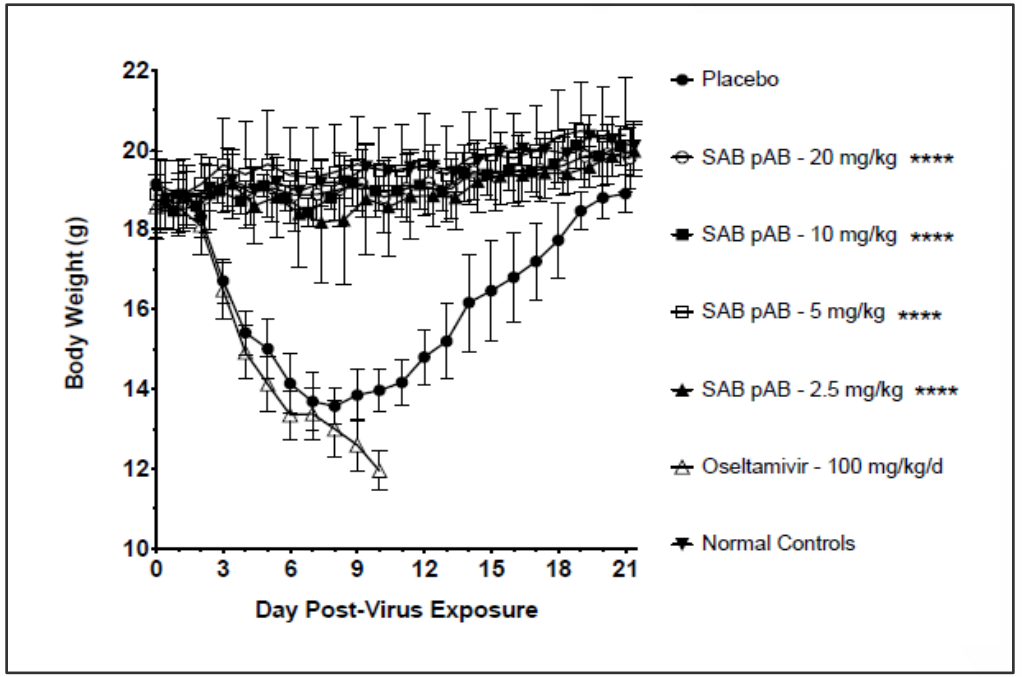
Oseltamivir Resistant H1N1pdm Virus Challenge Model

100% Protection with SAB-176 vs 0% Protection with 100mg/kg/d Oseltamivir



SAB-176 Protected Mice from Weight Loss While Oseltamivir Did Not



Study sponsored by NIAID/DMID and conducted by Utah State University

National Institute of Allergy and Infectious Diseases

UtahState University

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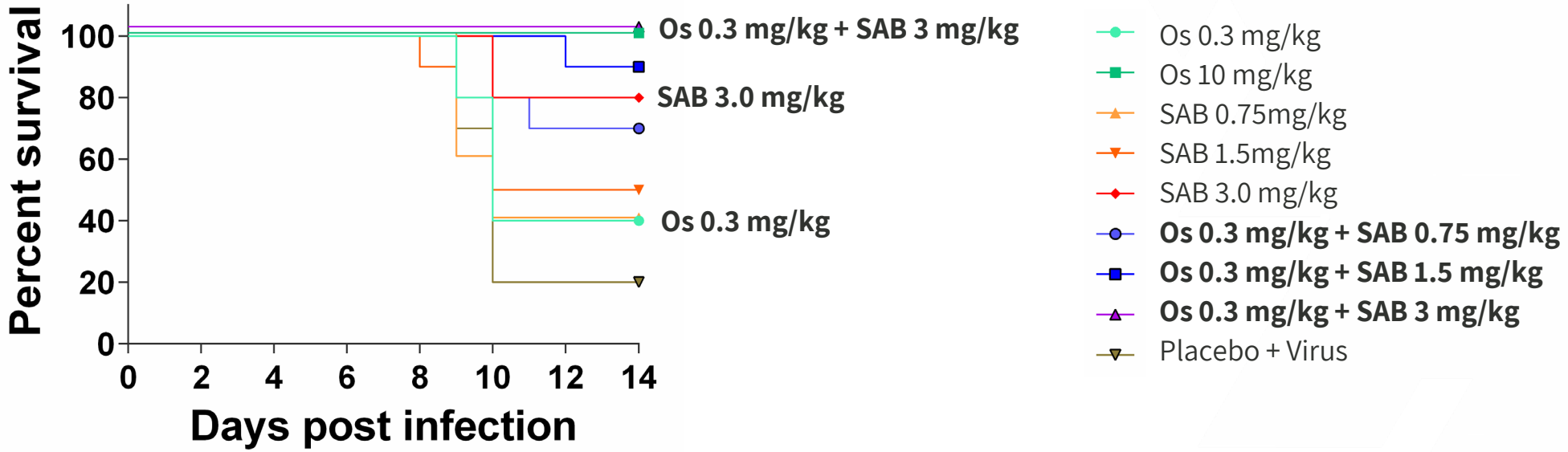
Potential Additive Efficacy of the Combination Therapy Approach Using SAB Anti-Influenza IgG Plus Oseltamivir

A combination of suboptimal doses of SAB and Oseltamivir provides additive protection in mice



Mice were infected with a mouse LD90 dose of pH1N1 and 12 h later received treatment as indicated.

- Oseltamivir (Os): 0.3 or 10 mg/kg/day administered in 2 doses per day for 5 days
- SAB-176-precursor (SAB): administered via IP injection one time at 0.75, 1.5 or 3.0 mg/kg

SAB 6 mg/kg provided 100% protection (data not shown)

National Institute of Allergy and Infectious Diseases

Icahn School of Medicine at Mount Sinai

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Conclusions

SAB-176: a novel anti-Type A and B influenza polyclonal immunotherapeutic

- Demonstrates significant HAI titers to multiple Type A and B influenza strains
- Met primary endpoint of reducing nasopharyngeal viral load as determined by qRT-PCR
- Met secondary endpoint of reducing symptoms
- Shortened the time of infectious viral shedding, as measured by inability to culture virus in vitro
- Demonstrated safety and efficacy in humans and potential synergy with oseltamivir in mice
- Future studies in high-risk patients are in development

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Next Step: Phase 2B SAB-176-202 Dose-Range Finding Trial

- **Trial design:** Phase 2B, Adaptive, Randomized, Double-Blind, Placebo-Controlled Dose-Range Finding Study to evaluate the safety and efficacy of two dose-levels of SAB-176 in patients with influenza at high risk of influenza complications

- **Target patient population:** Patients at high-risk for severe influenza complications based on the CDC high-risk definition, age ≥ 18years of age

- **Primary end point**: Time to Improvement of Influenza Symptoms (TTIIS). The end point has a regulatory precedent of a product approved and thus a Phase-3 grade end point

- **Study sample size and power**: 405 influenza patients randomized. The trial has two doses that could be declared significantly superior to the control. An equal split of the one-sided 0.10 type 1 error is used for each dose, with 0.05 for each dose

- **Treatment arms**: 1:1:1 randomization to SAB-176 high dose level, SAB-176 low dose-level, and PBO

- **Study flow:**
  - Emergency Department-based enrollment model previously funded by BARDA/ASPR will be implemented (Intravenous peramivir vs oral oseltamivir in high-risk emergency department patients with influenza: Results from a pilot randomized controlled study - PubMed (nih.gov))

- **Adaptive Design:** At each interim analysis the following adaptations are possible:
  1. Stop enrolling patients because one of the doses has demonstrated statistical superiority to the control;
  2. Stop enrolling patients for futility;
  3. Continue enrolling in the next hemisphere flu season but drop one of the dose arms;
  4. Continue enrolling the next hemisphere with both doses continuing in the trial.

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- Utah State University for conducting influenza mouse models.
- Naval Medical Research Command (NMRC) for HAI/MN analysis for the phase 1 and phase 2 clinical trials.
- PPD and hVIVO, PLC., for their work on the Phase 1 and Phase 2a clinical trials.