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Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts

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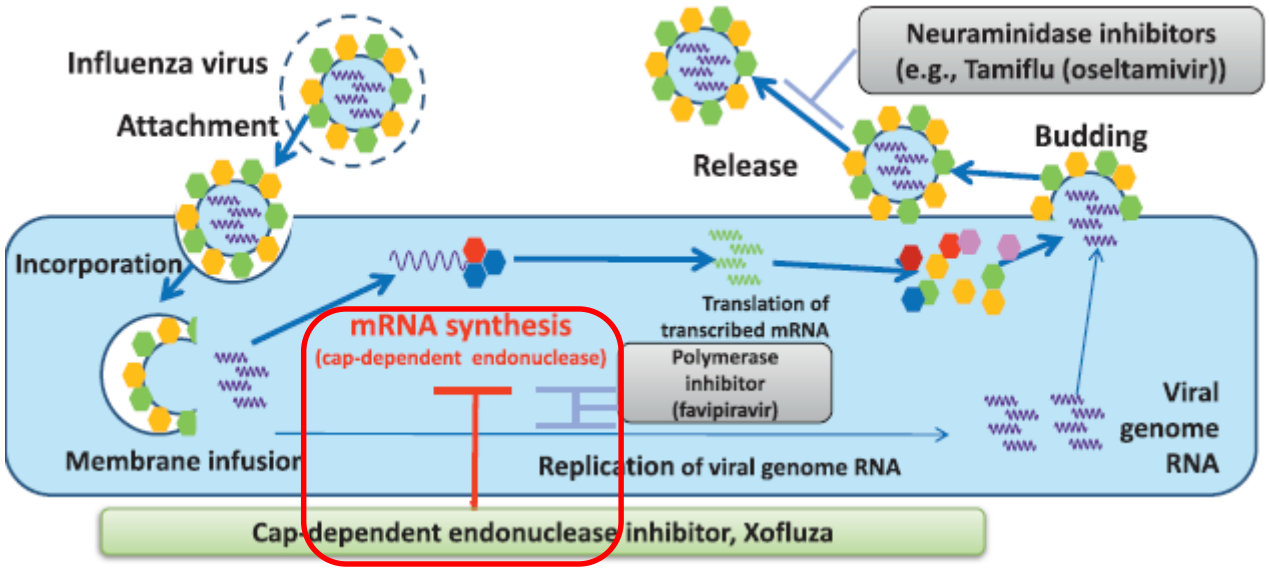
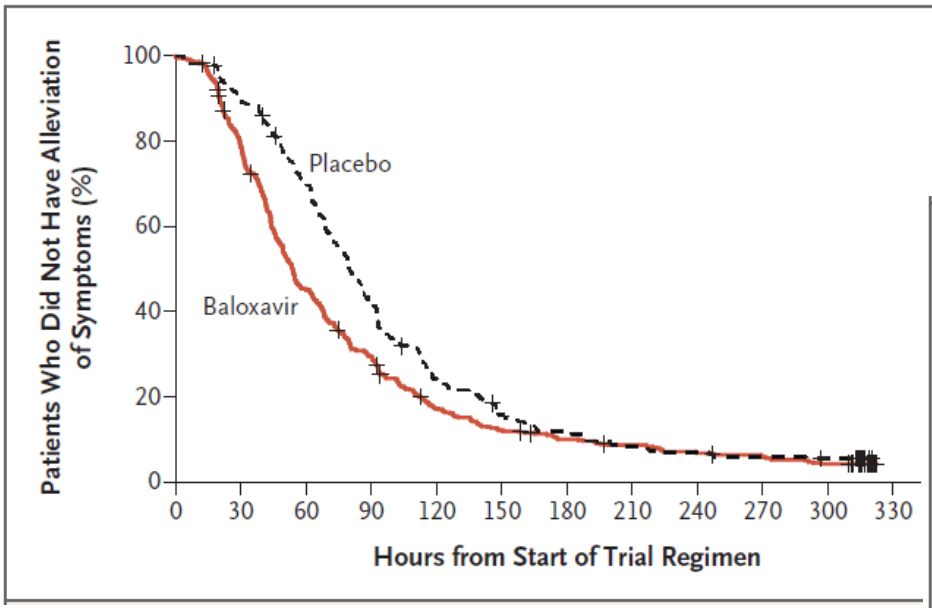
Silvio Ragozzino

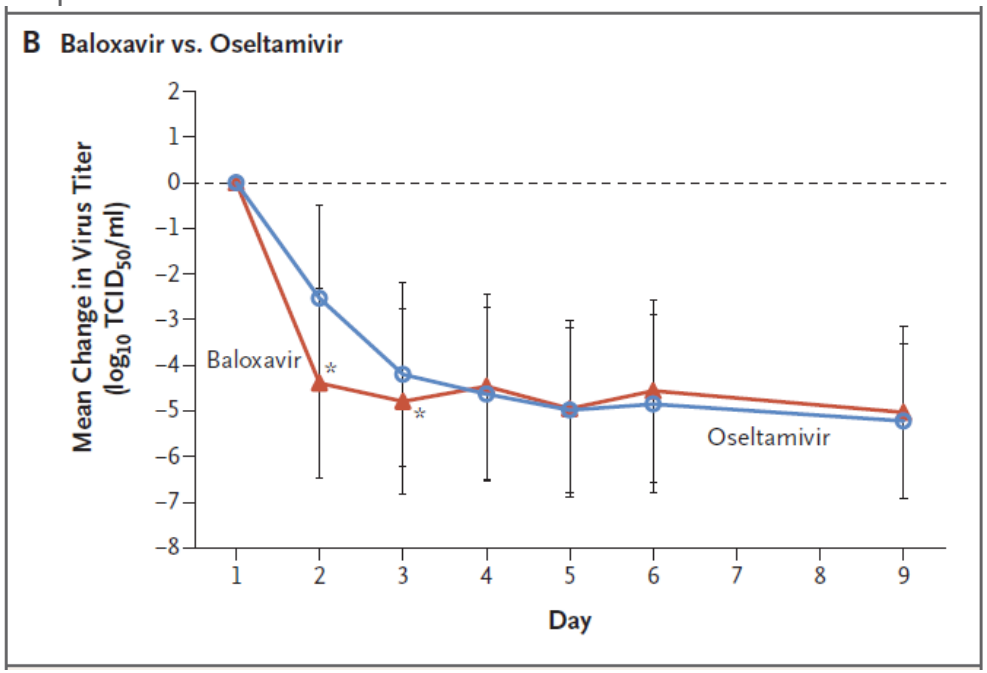
Background

- Households important sites for transmission of influenza virus
- Previous household-based trials showed that antiviral prophylaxis is effective
- Baloxavir marboxil



CAPSTONE-1





Hayden *et al*. N Eng J Med 2018

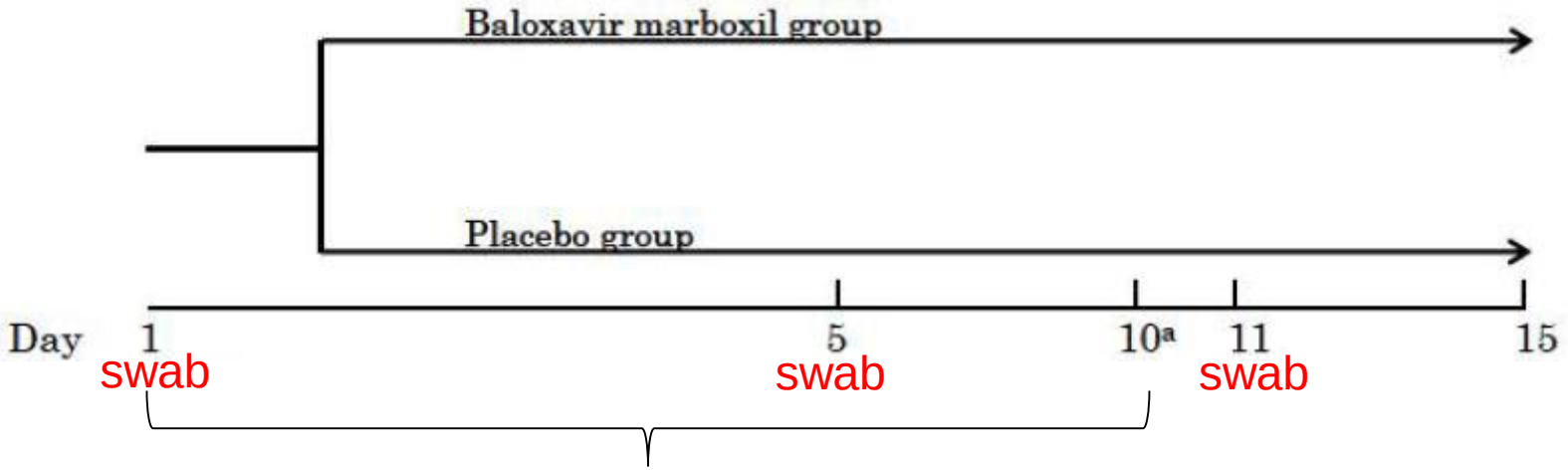
Baloxavir marboxil

- Single-dose treatment for uncomplicated influenza in US and Japan
- Emergence of variant viruses with mutations in the polymerase acidic protein (PA)
- **Aim**: to assess the efficacy of single-dose baloxavir for the prevention of influenza in household contacts

Study design

- Randomized, double-blind, placebo-controlled
- 52 primary care clinics in Japan; Nov 2018 – Mar 2019
- Sponsor: Shionogi (manufacturer of baloxavir)
- Trial population: Household contacts of index patients with influenza
  - ≥ 48 hours same household
  - No influenza symptoms
- Randomization 1:1 baloxavir or matching placebo with balancing of:
  - Time from illness onset in the index until IC of participant (<24h or ≥24h)
  - Treatment of index patient (baloxavir vs neuraminidase inhibitor)
  - Participant age (<12 or ≥12 years old)

Study design



Axillary temperature

Blood tests:
- Safety monitoring
- Antibody titers

Influenza symptoms:
- Cough
- Sore throat
- Headache
- Nasal discharge
- Feverishness or chills
- Muscle or joint pain
- Fatigue

4-point rating scale:
- 0 = absent
- 1 = mild
- 2 = moderate
- 3 = severe

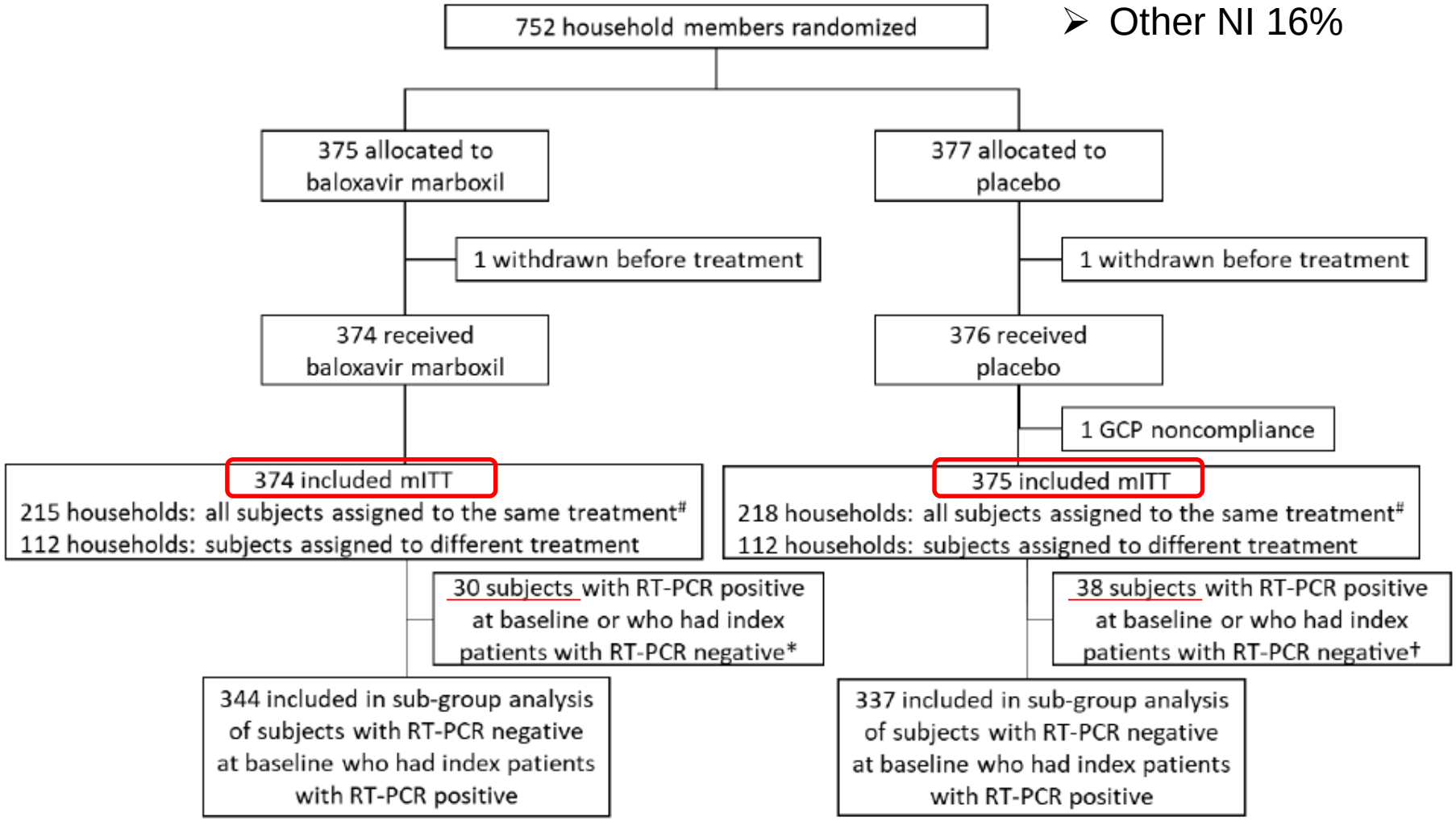
Study design

- Primary endpoint:
  - ➢Laboratory confirmed clinical influenza (fever ≥ 37.5°C and respiratory symptoms)
- Secondary endpoints:
  - ➢Laboratory confirmed illness (fever ≥ 37.5°C or respiratory symptoms)
  - ➢Positive PCR regardless of clinical manifestations
- Modified intention-to-treat population
- Participants with negative PCR at baseline and contact with a PCR-confirmed index patient
- Other prespecified subgroups (age, vaccination status, risk condition)
- Post hoc analyses (participants with any evidence of infection including seroconversion)

Results

545 index patients

Antiviral treatment:
- Baloxavir 53%
- Oseltamivir 31%
- Other NI 16%

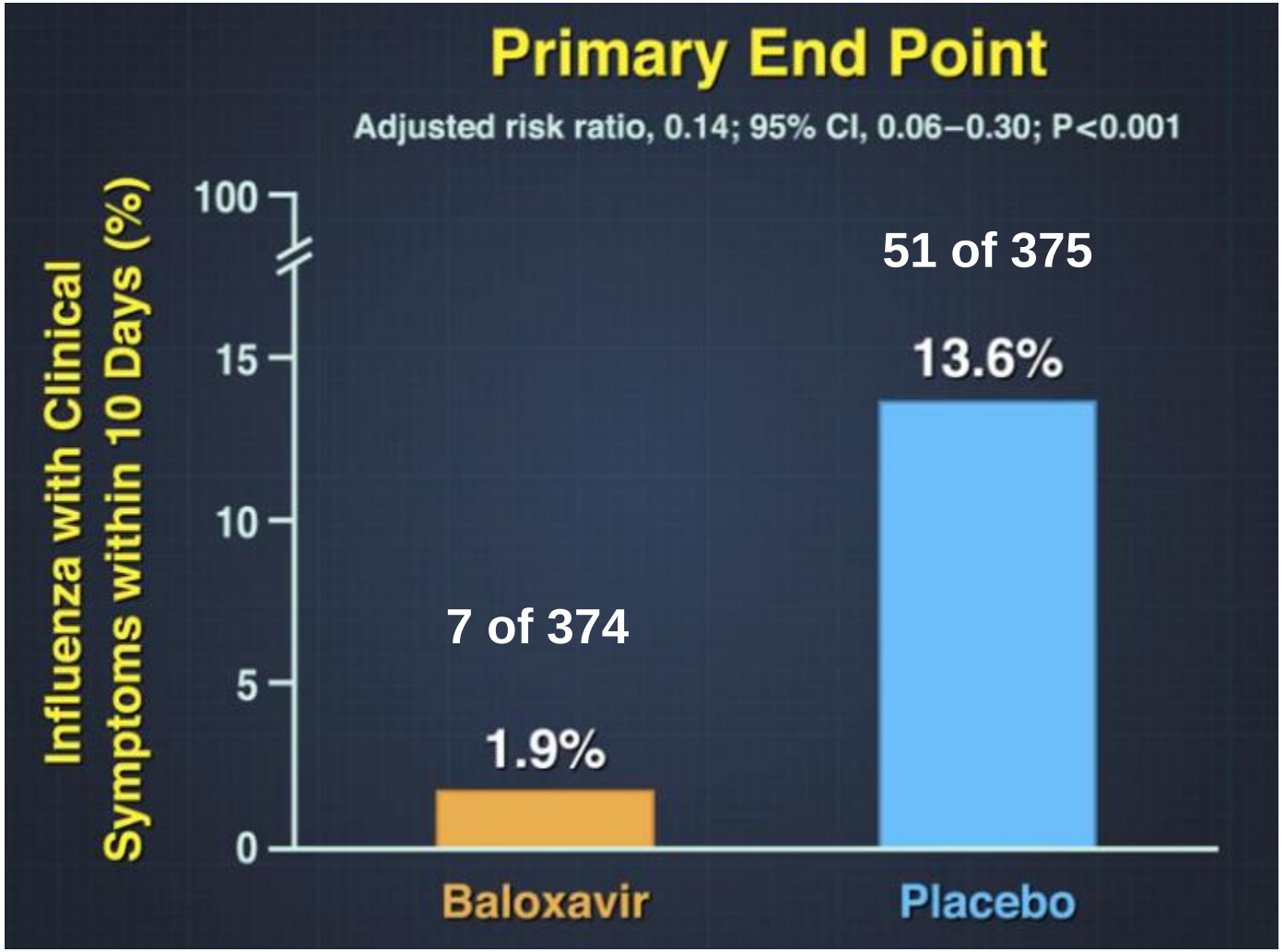


Results

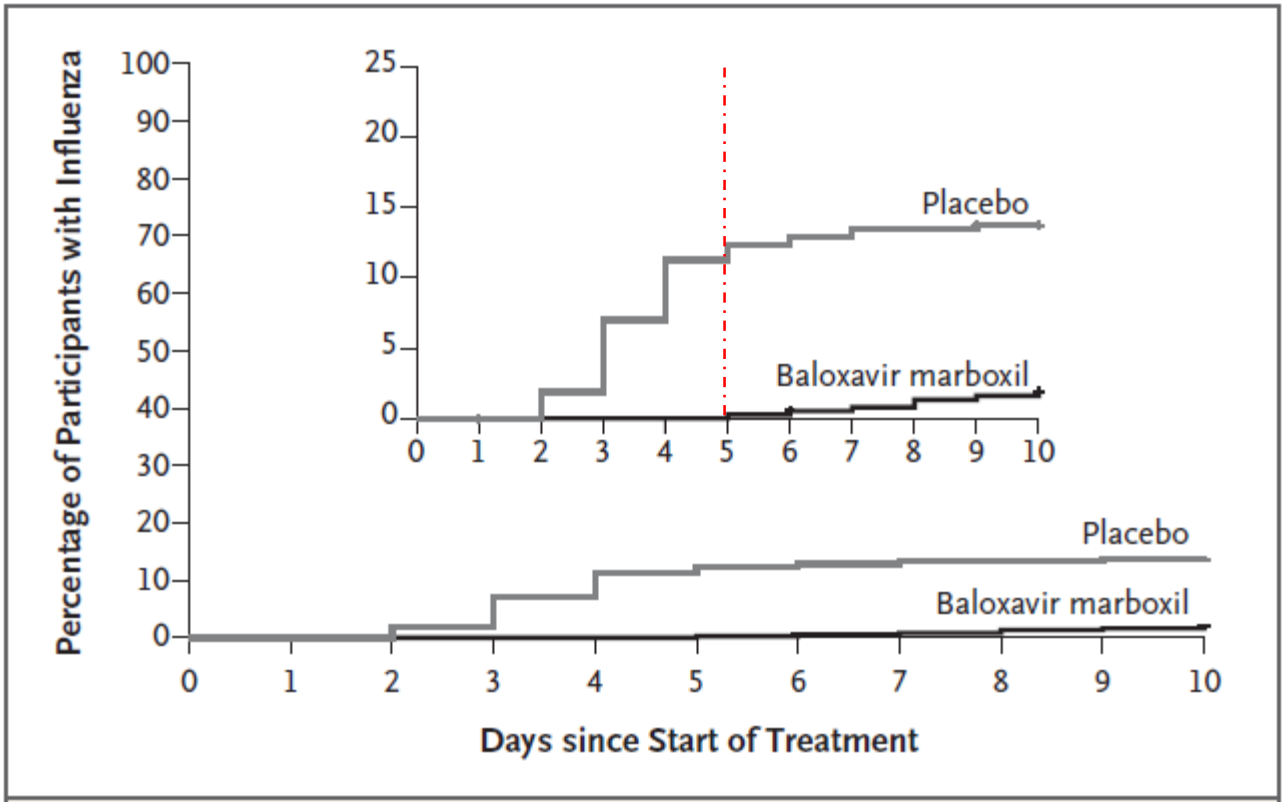
Table 1. Demographic and Baseline Characteristics of Index Patients and Participants.*

Characteristic	Index Patients (N = 545)†	Household Contacts	
		Baloxavir Marboxil (N = 374)	Placebo (N = 375)
Age			
Mean — yr	11.3±12.5	33.5±15.8	33.6±17.0
Distribution — no. (%)			
<6 yr	160 (29.4)	16 (4.3)	23 (6.1)
6–11 yr	241 (44.2)	55 (14.7)	48 (12.8)
12–19 yr	93 (17.1)	14 (3.7)	23 (6.1)
20–64 yr	43 (7.9)	281 (75.1)	266 (70.9)
≥65 yr	8 (1.5)	8 (2.1)	15 (4.0)
Influenza vaccination within previous 6 mo — no. (%)	170 (31.2)	131 (35.0)	124 (33.1)
Baseline influenza virus subtype as determined by RT-PCR assay — no. (%)			
A(H1N1)pdm09	255 (46.8)	2 (0.5)	11 (2.9)
A(H3N2)	265 (48.6)	16 (4.3)	16 (4.3)
A, not determined	1 (0.2)	8 (2.1)	9 (2.4)
B	5 (0.9)	0	0
Mixed infection	12 (2.2)	0	0
Negative	7 (1.3)	348 (93.0)	339 (90.4)
<24 Hr from onset of influenza symptoms in index patient to receipt of informed consent from participant — no. (%)	—	272 (72.7)	271 (72.3)

Results


Primary End Point
Adjusted risk ratio, 0.14; 95% CI, 0.06–0.30; P<0.001
Influenza with Clinical Symptoms within 10 Days (%)
100
15
10
5
0
7 of 374
1.9%
51 of 375
13.6%
Baloxavir
Placebo

Results



In the placebo group the illness occurred by day 5 in 90% of the cases

Among baseline positive participants, development of symptoms less often in the baloxavir arm (5/26; 19% vs. 21/36; 58%; aRR 0.34)

Results

Table 2. Primary and Secondary End Points (Modified Intention-to-Treat Population).*

End Point	Baloxavir Marboxil (N=374)		Placebo (N=375)		Adjusted Risk Ratio (95% CI)
	Participants with End Point	Percentage (95% CI)	Participants with End Point	Percentage (95% CI)	
	no./total no.		*no./total no.*		
Primary end point: laboratory-confirmed clinical influenza†					
In the modified intention-to-treat population	7/374	1.9 (0.8–3.8)	51/375	13.6 (10.3–17.5)	0.14 (0.06–0.30)‡
Among those who had a negative RT-PCR result at baseline and contact with a RT-PCR–positive index patient	5/344	1.5 (0.5–3.4)	39/337	11.6 (8.4–15.5)	0.13 (0.05–0.31)
Among those <12 yr of age	3/71	4.2 (0.9–11.9)	11/71	15.5 (8.0–26.0)	0.27 (0.08–0.90)
Among those ≥12 yr of age	4/303	1.3 (0.4–3.3)	40/304	13.2 (9.6–17.5)	0.10 (0.04–0.28)
Among those with underlying high-risk factors	1/46	2.2 (0.1–11.5)	8/52	15.4 (6.9–28.1)	0.13 (0.02–0.94)
Secondary end points					
RT-PCR–confirmed influenza virus infection regardless of fever and symptoms	49/374	13.1 (9.9–16.9)	114/375	30.4 (25.8–35.3)	0.43 (0.32–0.58)
RT-PCR–confirmed illness§	20/374	5.3 (3.3–8.1)	84/375	22.4 (18.3–27.0)	0.24 (0.15–0.38)
RT-PCR– or seroconversion-confirmed influenza virus infection regardless of fever and symptoms¶	59/374	15.8 (12.2–19.9)	119/375	31.7 (27.0–36.7)	0.50 (0.38–0.66)
RT-PCR– or seroconversion-confirmed illness‖	23/374	6.1 (3.9–9.1)	86/375	22.9 (18.8–27.5)	0.27 (0.17–0.42)
Asymptomatic infection confirmed by RT-PCR assay or seroconversion**	14/374	3.7 (2.1–6.2)	13/375	3.5 (1.9–5.9)	1.08 (0.52–2.27)

- Efficacy somewhat lower among <12 years (adjusted risk ratio 0.27 vs. 0.10)

Emergence of PA substituted variants

	Baloxavir (n=374)	Placebo (n=375)
Participants PCR (+) at any time	63	123
PA substitution I38T/M	10	2
Proportion among PCR (+)	15.9%	1.6%
Proportion in mITT population	2.7%	0.5%
PA substitution E23K	5	0
Proportion among PCR (+)	7.9%	-
Proportion in mITT population	1.3%	-

2 cases in the placebo group after rescue treatment with baloxavir

15 substituted variants in the baloxavir group:

- 4 baseline positive participants
- 4 index patient treated with neuraminidase inhibitors
- 7 transmission of substituted virus cannot be ruled out

Adverse events

Table 3. Incidence of Adverse Events (Safety Population).*

Event	Baloxavir Marboxil (N=374)	Placebo (N=375)
	number (percent)	
Any adverse event	83 (22.2)	77 (20.5)
Event reported in ≥1% of participants in either group		
Nasopharyngitis	24 (6.4)	25 (6.7)
Pharyngitis	4 (1.1)	1 (0.3)
Headache	8 (2.1)	6 (1.6)
Microscopic hematuria†	6 (1.6)	1 (0.3)
Increase in alanine aminotransferase level	4 (1.1)	1 (0.3)

Discussion

- Baloxavir effective and safe as prophylaxis against influenza in the household setting
- Baloxavir also reduced the risk of symptom development among those already infected at baseline
- Protective efficacy (86%)

Previous trials	Efficacy
Oseltamivir	68-89%
Zanamivir	82-84%
Laninamivir	46-78%

- Lower protective efficacy in pediatric patients as compared with teenagers and adults
- Non-household settings?
- Development of resistance and risk of prophylaxis failure

Limitations

- No follow-up samples in index patients → monitoring of resistant variants among index treated with baloxavir
- PA sequence not available for some patients with prophylaxis failure
- Prophylactic efficacy against influenza B not assessed because of limited circulation of the virus
- Industry sponsored (designed the trial, compiled the data, statistical analysis)