	Background	
Article	Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial	
Objective/Purpose	To assess the efficacy and tolerability of single-dose baloxavir treatment compared with placebo and oseltamivir in adult and adolescent outpatients with uncomplicated influenza who were at high risk of influenza-related complications	
Funding	Shionogi	
Brief Background	Influenza, better known as the flu, is an infectious and contagious family of viruses that consistently afflicts the world on a year-to-year basis. A 2018 study conducted by the Centers for Disease Control and Prevention (CDC) estimates that roughly 8% of the population get sick with influenza each season with a range of 3-11%, which varies based on the season.[2] For several years, the standard of care for outpatient influenza infections has been with oseltamivir (Tamiflu). This medication requires twice daily dosing for 5 days and has varying evidence regarding its overall efficacy.[3,4] Baloxavir marboxil (Xofluza) is a novel selective inhibitor of influenza cap-dependent endonuclease.[1] Previous studies have established baloxavir as an effective option in uncomplicated influenza infections which led to approval of the medication in the United States and Japan in 2018.[5] This trial was created too add to the overall evidence for use of antiviral medications in patients at high-risk of influenza complications as much of the available data for antiviral use is in healthy patients.[1]	
	Methods	
Outcome Measures	Primary: Time to improvement of influenza symptoms (TTIIS) of baloxavir marboxil versus placebo Secondary: TTIIS of baloxavir marboxil versus oseltamivir TTIIS of baloxavir marboxil versus placebo and oseltamivir in type of influenza infection *TTIIS defined as the time from the start of treatment to patient-reported improvement in all seven influenza-associated symptoms (cough, sore throat, headache, nasal congestion, feverishness/chills, muscle/joint pain, and fatigue)*	
Study Design	Phase 3, randomized, double-blind, double-dummy, placebo-controlled, active comparator study that was conducted at 551 sites in 17 countries and territories from January 2017 to March 2018.	
Target Population & Enrollment	Inclusion Criteria:	Exclusion Criteria:

	• Male or female patients $\geq$ 12 years old at high risk of developing influenza complications
	  ○ Defined by the CDC, e.g., Asthma or chronic lung disease, endocrine disorders, heart disease, age $\geq$ 65, or metabolic disorders
	• Diagnosis of influenza-like illness confirmed by:
	  ○ Fever $\geq$ 38°C (axillary)
	  ○ At least 1 of the 7 influenza-associated symptoms
	• Symptom duration of 48 hours or less
	• Women of childbearing potential who agrees to use a highly effective
		• Patients with severe influenza infection requiring inpatient treatment
		• Patients who previously received baloxavir marboxil
		• Patients weighing $\leq$ 40 kg
		• Women who are pregnant or breastfeeding
		• Patients with hepatic impairment
		• Patients with cancer in the last 5 years (excluding nonmelanoma skin cancer)
		• Patients with untreated HIV or a CD4 count < 350 cells/mm^3 in the last 6 months
		• Patients on immunosuppressive treatment for organ or bone marrow transplantation

<table>
<tr><td></td><td>method of contraception for 3 months after first dose of study drug[6]</td><td>• Patients exceeding 20 mg of prednisolone or equivalent dose of corticosteroid
• Patients with known creatinine clearance ≤ 60 mL/min</td></tr>
<tr><td>Treatment Groups</td><td colspan="2">Patients were randomized in a 1:1:1 fashion to receive:
• baloxavir marboxil 40 mg (wt. < 80 kg) or 80 mg (wt. ≥ 80 kg) once and oseltamivir-matched placebo twice daily for 5 days
• oseltamivir 75 mg twice daily for 5 days and a single dose of baloxavir-matched placebo at baseline
• single dose of baloxavir-matched placebo at baseline and oseltamivir-matched placebo twice daily for 5 days
Prior to randomization, patients were stratified by baseline Influenza Symptom Severity Scale, pre-existing and worsened symptoms at onset of illness compared with pre-influenza, region, and weight.</td></tr>
<tr><td>Statistical Analysis</td><td colspan="2">Power was set at 90% requiring 2,157 patients (719 per group).
Alpha set at 0.05.
Primary efficacy analysis was conducted in the modified intention-to-treat population (mITT) which included all patients who received at least one dose of the study drug, had a confirmed diagnosis of influenza based on RT-PCR positivity on day 1, and who were enrolled at sites with good clinical practice (GCP) compliance.
Generalized Wilcoxon test, with stratification, was used to compare the TTIIS between the baloxavir and placebo groups and baloxavir and oseltamivir groups.
Confidence intervals (CI) for median differences are bootstrap estimates from 10,000 bootstraps.
Kaplan-Meier Curves were used to estimate TTIIS.</td></tr>
<tr><td></td><td colspan="2">Results</td></tr>
<tr><td>Enrollment & Subjects Characteristics</td><td colspan="2">730 patients assigned to baloxavir, 388 included in analysis
729 patients assigned to placebo, 386 included in analysis
725 patients assigned to oseltamivir, 389 included in analysis
Total of 2,178 patients randomized, 1,163 included in analysis</td></tr>
<tr><td>Summary of Primary & Secondary Outcomes</td><td colspan="2">TTIIS Reduction in Baloxavir versus Placebo or Oseltamivir
<table>
<tr><th></th><th>Baloxavir (n=388)</th><th>Placebo (n=386)</th><th>Difference</th><th>P value</th></tr>
<tr><td>Median TTIIS (95% CI)</td><td>73.2 hours (67.2-85.1)</td><td>102.3 hours (92.7-113.1)</td><td>29.1 hours (14.6-42.8)</td><td><0.0001</td></tr>
<tr><th></th><th>Baloxavir (n=388)</th><th>Oseltamivir (n=389)</th><th>Difference</th><th>P value</th></tr>
<tr><td>Median TTIIS (95% CI)</td><td>73.2 hours (67.2-85.1)</td><td>81.0 hours (69.4-91.5)</td><td>7.7 hours (-7.9-22.7)</td><td>---</td></tr>
</table>
TTIIS Reduction in Baloxavir versus Placebo or Oseltamivir in influenza A or B infections
<table>
<tr><th></th><th>Baloxavir (n=182)</th><th>Placebo (n=185)</th><th>Difference</th><th>P value</th></tr>
<tr><td>Median TTIIS in Influenza A H3N2 infection (95% CI)</td><td>75.4 hours (62.4-91.6)</td><td>100.4 hours (88.4-113.4)</td><td>25.0 hours (4.7-45.2)</td><td>0.014</td></tr>
<tr><th></th><th>Baloxavir (n=167)</th><th>Placebo (n=168)</th><th>Difference</th><th>P value</th></tr>
</table></td></tr>
</table>

	Median TTIIS in Influenza B infection (95% CI)	74.6 hours (67.4-90.2)	100.6 hours (82.8-115.8)	26.0 hours (2.7-43.6)	0.014
		Baloxavir (n=182)	**Oseltamivir (n=190)**	**Difference**	**P value**
	Median TTIIS in Influenza A H3N2 infection (95% CI)	75.4 hours (62.4-91.6)	68.2 hours (53.9-81.0)	-7.2 hours (-31.5-14.5)	---
		Baloxavir (n=167)	**Oseltamivir (n=149)**	**Difference**	**P value**
	Median TTIIS in Influenza B infection (95% CI)	74.6 hours (67.4-90.2)	101.6 hours (90.5-114.9)	27.1 hours (6.9-42.3)	0.025
Safety	Adverse effects were similar between all 3 groups with the most frequently identified as bronchitis, sinusitis, diarrhea, and nausea. Adverse events that lead to withdrawal of the study in more than one patient was pneumonia (baloxavir=2; oseltamivir=1), vomiting (baloxavir=2), bronchitis (placebo=2). Serious adverse events were reported more in the placebo and oseltamivir group versus baloxavir (9, 8, and 5 respectively). One patient in the oseltamivir group developed pneumonia on study day 12 leading to death on day 38.				
	Discussion				
Author's Conclusion	The administration of single dose baloxavir marboxil within 48 hours of symptom onset was shown to have quicker reduction in TTIIS than placebo in adolescent and adult patients at high-risk for influenza complications, whereas baloxavir was shown to have similar efficacy in reducing TTIIS as oseltamivir.				
Strengths	Randomization resulted in similar groups with pre-randomization stratification. Double-blinded with double-dummy. Broad inclusion criteria allows results to apply to a large variety of patients. Excluded patients who were enrolled at sites that did not meet GCP compliance. Included patients over the age of 65.				
Limitations	Power was not met Excluded patients will require further studies for safety and efficacy. Regional differences were identified in the TTIIS between baloxavir and placebo groups with potential to lead to different outcomes (Asia versus North America and Europe [baseline, time to treatment, and incidence of metabolic disorders]). Study was not powered to compare baloxavir with oseltamivir with respect to influenza type.				
Presenter's Conclusion	This was a high-quality study that showed a statistically significant reduction in TTIIS with single dose baloxavir versus placebo, but it did not show that baloxavir was superior in TTIIS reduction to oseltamivir. the CAPSTONE-2 trial did not meet power; however, this was due to excluding patients who were at non-compliant sites. This trial establishes that baloxavir should be considered for adolescent and adult patients at high-risk of developing influenza complications if administered within 48 hours of symptom onset. Based off of the efficacy, safety profile, and one-time dosing associated with baloxavir, I think that this medication can also be considered for use with patients at a low-risk of developing complications. There are some concerns with baloxavir that this trial does not address. A major concern that is not addressed in this trial is cost. Baloxavir is currently only available as a name brand medication with a cost of $185.40/tablet (either strength). Compared to oseltamivir with a cost per capsule for the generic and brand name of $15.44-$15.46 and $18.23 respectively. There is a manufacturer				

	coupon available for Xofluza that pays a max of $60 for a fill. Clinicians should consider the patient's insurance status, insurance formulary, and other patient specific factors (e.g., weight, ability to swallow tablets/capsules, and adherence risks) prior to prescribing.
Recommendation	I recommend the use of baloxavir marboxil in adolescent and adult outpatients at high-risk of influenza complications due to the quicker symptom reduction versus placebo, broad inclusion criteria, and similar efficacy to oseltamivir. The ability to take a one-time dose with similar efficacy and adverse effects to a twice daily dosed medication requiring 5 days of therapy outweighs this lack of statistically significant difference between the medications.

References:

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2. Tokars JI, Olsen SJ, Reed C. Seasonal Incidence of Symptomatic Influenza in the United States. *Clin Infect Dis*. 2018;66(10):1511-1518. doi:10.1093/cid/cix1060
3. Dobson J, Whitley RJ, Pocock S, Monto AS. Oseltamivir treatment for influenza in adults: a meta-analysis of randomised controlled trials [published correction appears in Lancet. 2015 May 2;385(9979):1728] [published correction appears in Lancet. 2015 May 2;385(9979):1728]. *Lancet*. 2015;385(9979):1729-1737. doi:10.1016/S0140-6736(14)62449-1
4. Ebell MH, Call M, Shinholser J. Effectiveness of oseltamivir in adults: a meta-analysis of published and unpublished clinical trials. *Fam Pract*. 2013;30(2):125-133. doi:10.1093/fampra/cms059
5. Hayden FG, Sugaya N, Hirotsu N, et al. Baloxavir Marboxil for Uncomplicated Influenza in Adults and Adolescents. *N Engl J Med*. 2018;379(10):913-923. doi:10.1056/NEJMoa1716197
6. https://clinicaltrials.gov/ct2/show/NCT02949011