Drugs (2018) 78:693–697
https://doi.org/10.1007/s40265-018-0899-1

ADISINSIGHT REPORT

# Baloxavir: First Global Approval

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Published online: 5 April 2018


**Abstract** Baloxavir marboxil (Xofluza™; baloxavir) is an oral cap-dependent endonuclease inhibitor that has been developed by Roche and Shionogi. The drug blocks influenza virus proliferation by inhibiting the initiation of mRNA synthesis. In February 2018, baloxavir received its first global approval in Japan for the treatment of influenza A or B virus infections. Phase III development is underway in the USA, EU and other countries for this indication. This article summarized the milestones in the development of baloxavir leading to this first global approval for influenza A or B virus infections.

## 1 Introduction

Epidemic and pandemic influenza are major public health concerns and vaccination remains the primary method to prevent influenza [1, 2]. Influenza antiviral drugs are typically used to treat newly emerged or variant viruses due to their ability to target conserved parts of the virus [2]. In some countries including the USA and Japan, such drugs are widely used to treat seasonal influenza in otherwise healthy patients. With growing concerns of resistance development to currently available influenza antivirals (i.e. adamantanes and neuraminidase inhibitors), new antiviral drugs with different mechanisms of action are currently undergoing clinical trials [2].

Baloxavir marboxil (Xofluza™; baloxavir) is a novel, cap-dependent endonuclease inhibitor that has been developed for the treatment of influenza A or B [3]. Unlike neuraminidase inhibitors that impair viral release from infected host cells [2], baloxavir blocks influenza virus proliferation by inhibiting the initiation of mRNA synthesis [3]. On 23 February 2018, baloxavir received its first global approval in Japan for the treatment of influenza A or B virus infections in paediatric and adult patients [3, 4]. For this indication, a single oral dose of baloxavir is recommended to be taken as soon as possible after onset of symptoms [3]. The dosage strength can be adjusted according to bodyweights in adults and children aged $\geq$ 12 years (40 or 80 mg), as well as in children aged $<$12 years (10, 20 or 40 mg) [3]. Phase III development in the USA, EU and other countries is underway for the treatment of influenza A or B virus infections. Baloxavir is also in preclinical development for influenza A virus H5N1 subtype in Japan.

### 1.1 Company Agreements

In February 2016, Shionogi entered into a global licensing and collaboration agreement with Roche, for the development and commercialization of baloxavir [5]. Under the terms of the agreement, Shionogi receives an upfront payment and is eligible to receive additional milestone payments (related to development and commercialization) and royalties of baloxavir sales from Roche. Roche has the global right to commercialize baloxavir (except in Taiwan and Japan where Shionogi holds the full rights), with Shionogi retaining certain co-promotion rights in the USA [5].

This profile has been extracted and modified from the *AdisInsight* database. *AdisInsight* tracks drug development worldwide through the entire development process, from discovery, through pre-clinical and clinical studies to market launch and beyond.

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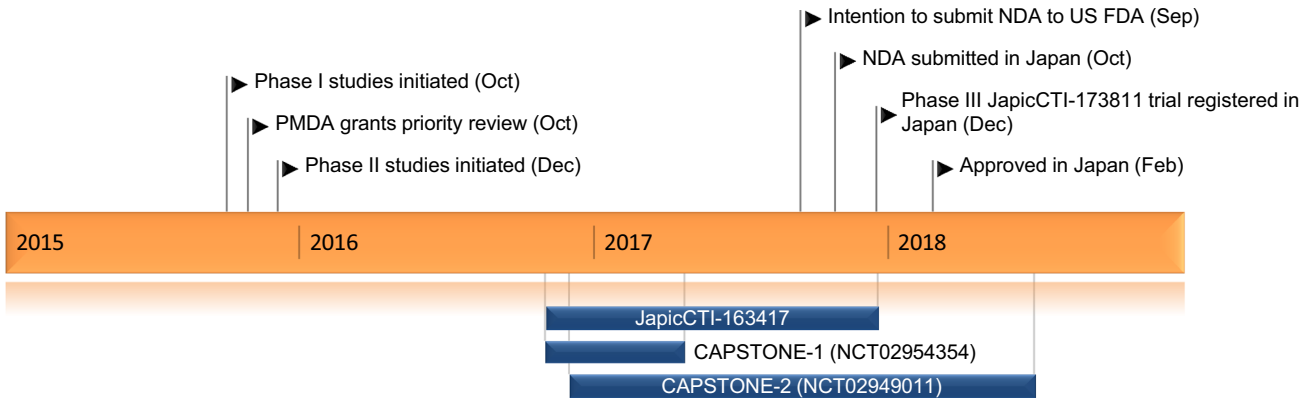



Key milestones in the development of baloxavir marboxil, focussing on phase III clinical trials. *NDA* new drug application, *PMDA* pharmaceuticals and medical devices agency

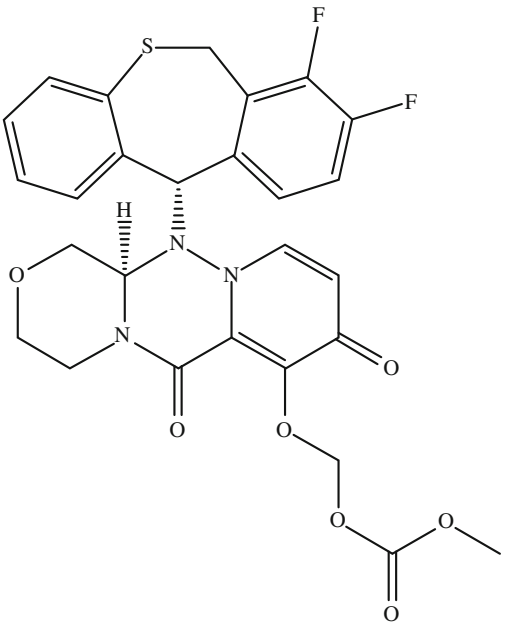
## 2 Scientific Summary

### 2.1 Pharmacodynamics

Baloxavir is a small molecule selective inhibitor of cap-dependent endonuclease, a key enzyme in influenza viruses for initiating mRNA synthesis [6]. S-033447, the active form of baloxavir demonstrated antiviral activity against influenza A and B laboratory virus strains and clinical isolates (including the NA/H274Y mutant strain) [3]. In these assays, the concentration to suppress viral titer to 90% ($EC_{90}$) was 0.46–0.98 nmol/L for influenza A and 2.21–6.48 nmol/L for influenza B [3]. In vitro and in vivo, baloxavir also showed significant antiviral activity against other influenza strains, including H5N1 and H7N9 subtype avian influenza virus strains and influenza A and B strains resistant to oseltamivir [3, 7] and demonstrated synergistic antiviral activity with neuraminidase inhibitors (e.g. oseltamivir, zanamivir) [8].

In mouse models inoculated with clinical isolates or laboratory strains of influenza A or B viruses (including oseltamivir-resistant strains and the H5N1 and H7N9 subtypes), single day dosing of baloxavir (5–50 mg/kg twice in 1 day) improved mortality compared with a clinically equivalent dose of oseltamivir (5 mg/kg, twice daily for 5 days) [3, 7, 9]. Baloxavir was associated with a profound viral titer reduction within 24 h of administration compared with oseltamivir; viral titers decreased in a dose-dependent manner [6, 7, 9]. The efficacy of baloxavir in a mouse model was evident, even when treatment initiation was delayed by 24–96 h after inoculation of a lethal quantity of influenza A virus [3, 10]. Both the delayed administration of baloxavir or coadministration of baloxavir with oseltamivir significantly improved mortality compared with oseltamivir monotherapy [10].

In in vitro tolerance isolation tests with laboratory isolates of influenza A and B virus strains, the presence of an I38T amino acid mutation in the polymerase acidic protein region (the binding target site of baloxavir) reduced susceptibility to baloxavir ≈ 100-fold [3].



Chemical structure of baloxavir marboxil

### 2.2 Pharmacokinetics

When a single oral dose of baloxavir 40 mg was administered to healthy male subjects in the fasting state, peak plasma concentrations ($C_{max}$) of baloxavir were below the limit of detection, as the drug quickly undergoes hydrolysis to its active form, S-033447 [3]. The $C_{max}$ of S-033447 is reached within a median of 4 h [3]. S-033447 displays

linear, dose-proportional systemic exposure [i.e. $C_{max}$ and area under the plasma concentration–time curve (AUC)] across a single dose range of 6–80 mg in healthy adult subjects [11]. Food appear to decrease baloxavir exposure but the prescribing information contains no specific recommendations pertaining to baloxavir administration with food [3].

S-033447 is highly (93–94%) protein bound [3] and has a large apparent volume of distribution (494–655 L) [11]. S-033447 is primarily metabolized by UGT1A3 to glucuronic acid conjugate and subsequently metabolized by CYP3A to form sulfoxide [3]. Baloxavir is primarily eliminated by biliary excretion. Following a single dose of radiolabelled baloxavir (40 mg) in healthy subjects, 80% of the drug was recovered in the faeces and 15% was recovered in the urine. The estimated mean elimination half-life of S-033447 was 96 h [3].

Studies show that dosage adjustments are required according to bodyweight [3]. In the phase III clinical trials (Sect. 2.3), baloxavir exposure was similar when a single oral bodyweight-adjusted dose of baloxavir was administered to adults and paediatric patients [3].

Based on in vitro studies, baloxavir and S-033447 are substrates of P-glycoprotein (P-gp) [3]. In addition, baloxavir weakly inhibits P-gp, CY2B6, CYP2C8 and CYP3A and S-033447 inhibits P-gp and breast-cancer-receptor protein; however, these interactions are not expected to be clinically relevant [3].

### 2.3 Therapeutic Trials

A single oral dose of baloxavir significantly improved virologic outcomes compared with placebo and oseltamivir in adult and adolescent patients with influenza A or B virus infections in the randomized, double-blind, placebo- and active-controlled, phase III, CAPSTONE-1 trial (NCT02954354) [12]. The trial enrolled adults and children (aged 12–64 years) who were diagnosed with uncomplicated influenza A or B (i.e. fever $\geq 38$ °C, $\geq 1$ general symptoms and $\geq 1$ respiratory symptoms related to influenza); time from symptom of onset was $\leq 48$ h. Patients ($n = 1436$) received a single dose of baloxavir (40 or 80 mg), placebo or oseltamivir 75 mg twice daily for 5 days [12, 13].

In CAPSTONE-1, the time to alleviation of influenza symptoms (primary endpoint) was significantly shorter in baloxavir than placebo recipients (53.7 vs. 80.2 h; $p < 0.0001$) [12]. Moreover, the median time to cessation of viral shedding was significantly shorter with baloxavir than with placebo (24 vs. 96 h; $p < 0.0001$) or oseltamivir (24 vs. 72 h; $p < 0.0001$). Patients receiving baloxavir had significantly greater reductions from baseline in viral titer and RNA content than those receiving placebo (until day 5) or oseltamivir (until day 3) [12].

Baloxavir was more effective than placebo in alleviating influenza symptoms in a phase II proof-of-concept, randomized, dose-finding trial in adults (aged 20–64 years; $n = 400$) with uncomplicated influenza A or B (JapicCTI-153090) [6]. Patients who received a single dose of baloxavir (10, 20, or 40 mg) within 48 h of symptom onset had significant reductions in time to alleviation of seven major influenza symptoms (49.5–54.2 vs. 77.7 h; $p \leq 0.0182$) and in time to resolution of fever (28.9–33.4 vs. 45.3 h; $p \leq 0.0001$) compared with those receiving placebo. A significant viral load reduction was also observed in the baloxavir group at 24 and 48 h post dose

Features and properties of baloxavir

| | |
|---|---|
| Alternative names | RG 6152; S 033188; XOFLUZA |
| Class | Antivirals; dibenzothiepins; esters; pyridines; triazines; small molecules |
| Mechanism of action | Cap-dependent endonuclease inhibitor |
| Route of administration | Oral |
| Pharmacodynamics | Blocks cap-dependent endonuclease, inhibiting the initiation of mRNA synthesis and reduce virus proliferation |
| Pharmacokinetics | Median time to $C_{max}$ 4 h; mean elimination half-life 96 h |
| Adverse events | |
| Most frequent (> 1%) | Diarrhoea |
| ATC codes | |
| WHO ATC code | J05 (antivirals for systemic use) |
| EphMRA ATC code | J5 (antivirals for systemic use) |
| Chemical name | Carbonic acid, (((12aR)-12-((11S)-7,8-difluoro-6,11-dihydrodibenzo(b,E)thiepin-11-yl)-3,4,6,8,12,12a-hexahydro-6,8-dioxo-1H-(1,4)oxazino(3,4-C)pyrido(2,1-F)(1,2,4)triazin-7-yl)oxy)methyl methyl ester |

Key clinical trials of baloxavir

| Drug(s) | Indication | Phase | Status | Location(s) | Identifier | Sponsor(s) |
|---|---|---|---|---|---|---|
| Baloxavir, placebo, oseltamivir | Influenza A or B in otherwise healthy adults and children (aged ≥ 12 years) | 3 | Completed | US, Canada, Japan | NCT02954354 (CAPSTONE-1) | Shionogi |
| Baloxavir | Influenza A or B in otherwise healthy paediatric patients (aged < 12 years) | 3 | Completed | Japan | JapicCTI-163417 | Shionogi |
| Baloxavir, placebo, oseltamivir | Influenza A or B in adults and children (aged ≥ 12 years) with high risk of influenza complications | 3 | Recruiting | Multinational | NCT02949011; EudracCT2016-002688-32 (CAPSTONE-2) | Shionogi |
| Baloxavir 2% granules | Influenza A or B in otherwise healthy paediatric patients (aged < 12 years) | 3 | Recruiting | Japan | JapicCTI-173811 | Shionogi |
| Baloxavir, placebo | Influenza A or B in otherwise healthy adults | 2 | Completed | Japan | JapicCTI-153090 | Shionogi |

(vs. placebo; $p < 0.001$ for all doses). A single dose of baloxavir 40 mg was associated with significantly shorter time to alleviation of individual systemic (e.g. feverishness/chills, headache, fatigue, aches and pains) and respiratory (e.g. nasal congestion) symptoms compared with placebo ($p \leq 0.0463$) [6].

The efficacy of baloxavir in paediatric patients (aged < 12 years) with uncomplicated influenza A or B was shown in a single-arm study (JapicCTI-163417) [3]. Patients received a single dose of baloxavir 10, 20 or 40 mg ($n = 29$, 65 and 8) within 48 h of symptom onset; doses were bodyweight-adjusted. The time to alleviation of influenza symptoms in all patients was 39.1–60.9 h [3].

### 2.4 Adverse Events

In CAPSTONE-1, a single dose of baloxavir was generally well tolerated in adults and children aged ≥ 12 years with influenza A or B [12]. Adverse events (AEs) were reported in 20.7% of baloxavir recipients, 24.6% of placebo recipients and 24.8% of oseltamivir recipients. Significantly fewer baloxavir than oseltamivir recipients reported treatment-related AEs ($p = 0.0088$) [13].

A single dose of baloxavir was well tolerated in clinical trials in adults and children with influenza A or B. The incidence of AEs in the safety population was 5.4% in clinical trials in adults and children aged ≥ 12 years ($n = 910$) and 3.8% in clinical trials in children aged < 12 years ($n = 105$) [3]. The most common AE was diarrhoea. Other reported AEs (incidence < 1%) were headache and increased ALT and AST [3].

### 2.5 Ongoing Clinical Trials

In December 2016, Shionogi commenced recruitment for a randomized, multinational, double-blind phase III trial (CAPSTONE-2; NCT02949011) which will evaluate the efficacy of baloxavir versus placebo and oseltamivir for the treatment of influenza A or B in adults and children (aged ≥ 12 years) with high risk factors for influenza complications (e.g. those with asthma, chronic lung disease, heart disease or compromised immune system, aged ≥ 65 years, or with endocrine, metabolic, blood or neurological disorders) [14]. Patients will receive a single dose of baloxavir (40 or 80 mg), placebo or oseltamivir 75 mg twice daily for 5 days within 48 h of symptom onset. The primary endpoint is the time to improvement of symptoms from treatment initiation [14].

In December 2017, Shionogi initiated an open-label, phase III trial (JapicCTI-173811) to evaluate the pharmacokinetics, safety and efficacy of a single dose of baloxavir 2% granules in otherwise healthy paediatric patients (aged < 12 years) with influenza A or B [15]. Enrolled patients are required to weigh < 20 kg within symptom onset of ≤ 48 h. Patients will receive a single bodyweight-adjusted dose of baloxavir [15].

## 3 Current Status

Baloxavir received its first global approval on 23 February 2018 in Japan for the treatment of influenza A or B in otherwise healthy adult and paediatric patients [3, 4].

#### Compliance with Ethical Standards

**Funding** The preparation of this review was not supported by any external funding.

**Conflict of interest** During the peer review process the manufacturer of the agent under review was offered an opportunity to comment on the article. Changes resulting from any comments received were made by the author on the basis of scientific completeness and accuracy. Young-A Heo is a salaried employee of Adis/Springer, is responsible for the article content and declares no relevant conflicts of interest.

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