IQWiG Reports – Commission No. A21-22

Baloxavir marboxil (post-exposure prophylaxis of influenza) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Baloxavir marboxil (Postexpositionsprophylaxe der Influenza) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 12 May 2021). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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[2] Table numbers start with “2” as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
C_{24}	plasma concentration after 24 hours
C_{240}	plasma concentration after 240 hours
C_{72}	plasma concentration after 72 hours
C_{max}	maximum plasma concentration
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PEP	post-exposure prophylaxis
RCT	randomized controlled trial
RT-PCR	reverse transcriptase polymerase chain reaction
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug baloxavir marboxil. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 12 February 2021.

Research question

The aim of the present report is the assessment of the added benefit of baloxavir marboxil in comparison with the appropriate comparator therapy (ACT) for post-exposure prophylaxis (PEP) of influenza in adult and adolescent patients aged 12 years and above.

In its specification of the ACT, the G-BA differentiated between 2 patient groups in the approved therapeutic indication. This resulted in 2 research questions for the assessment; their subindications and ACTs are presented in Table 2.

Table 2: Research questions of the benefit assessment of baloxavir marboxil

Research question	Subindication	ACT[a]
1	Adult and adolescent patients aged 12 years and above with influenza exposure without risk of influenza-related complications	Watchful waiting
2	Adult and adolescent patients aged 12 years and above with influenza exposure with risk of influenza-related complications	Antiviral therapy (oseltamivir or zanamivir)[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Official recommendations, epidemiological variability and the impact of the disease in different geographical regions and patient groups should be taken into account when using antiviral drugs for the post-exposure prophylaxis of influenza.

ACT: appropriate comparator; G-BA: Federal Joint Committee

The term "patient" includes all individuals with exposure to influenza. In the following, the term "individuals" is used.

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: individuals aged 12 years and above with influenza exposure without risk of influenza-related complications
- Research question 2: individuals aged 12 years and above with influenza exposure with risk of influenza-related complications

Research questions 1 and 2 of the present benefit assessment correspond to the patient groups a and b in the G-BA's specification of the ACT.

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) were used for the derivation of the added benefit. This corresponds to the inclusion criteria of the company for research question 1. The company did not describe any inclusion criteria for research question 2.

Research question 1: individuals aged 12 years and above with influenza exposure without risk of influenza-related complications

Study pool and study characteristics

The BLOCKSTONE study is a double-blind RCT comparing baloxavir marboxil with placebo, conducted exclusively in individuals of Asian family origin.

The study included only adults and children who had contact in their own household with a patient who had influenza (hereinafter referred to as "index patient"). All index patients received antiviral therapy after study inclusion. The individuals examined in the BLOCKSTONE study were those who had contact with the index patients and were thus exposed to the influenza virus. The individuals had lived in the same household as the index patient for 48 hours or more prior to informed consent. At enrolment, the individuals were not allowed to have influenza symptoms such as fever or cough. 375 individuals were randomized to the intervention arm and 377 to the comparator arm.

In accordance with the approval, only the subpopulation aged ≥ 12 years and without risk of influenza-related complications is relevant for research question 1. A total of 549 individuals correspond to the relevant subpopulation, of which 275 individuals in the intervention arm and 274 individuals in the comparator arm.

Baloxavir marboxil was administered in compliance with the Summary of Product Characteristics (SPC). Individuals in the comparator arm received matching placebo. The ACT was adequately implemented in the BLOCKSTONE study.

Primary outcome of the study was symptomatic influenza (fever and respiratory symptom) confirmed by reverse transcriptase polymerase chain reaction (RT-PCR). Further patient-relevant outcomes on morbidity and side effects were additionally recorded.

Risk of bias and certainty of conclusions of the results

The risk of bias across outcomes for the BLOCKSTONE study was rated as low. The outcome-specific risk of bias for all outcomes used in the dossier assessment was also rated as low.

Results

Mortality

All-cause mortality

No death occurred in the BLOCKSTONE study. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with watchful waiting; an added benefit is therefore not proven.

Morbidity

Symptomatic influenza infection

A statistically significant difference in favour of baloxavir marboxil in comparison with placebo was shown for the outcome "symptomatic influenza infection". There was an indication of an added benefit of baloxavir marboxil in comparison with watchful waiting.

Health-related quality of life

No outcomes in the outcome category "health-related quality of life" were recorded in the BLOCKSTONE study. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with watchful waiting in this outcome category; an added benefit is therefore not proven.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between baloxavir marboxil and placebo for either of the outcomes "serious adverse events (SAEs)" and "discontinuation due to adverse events (AEs)". This resulted in no hint of greater or lesser harm from baloxavir marboxil in comparison with watchful waiting; an added benefit is therefore not proven.

Research question 2: individuals aged 12 years and above with influenza exposure with risk of influenza-related complications

The company did not present any data for the assessment of the added benefit of baloxavir marboxil in comparison with the ACT for adult and adolescent patients aged 12 years and above with influenza exposure with risk of influenza-related complications. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with the ACT. An added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Research question 1: individuals aged 12 years and above with influenza exposure without risk of influenza-related complications

Based on the results presented, probability and extent of the added benefit of the drug baloxavir marboxil in comparison with the ACT are assessed as follows:

In the overall picture, there is exclusively one positive effect of considerable extent for the outcome "symptomatic influenza infection" for individuals aged 12 years and above with influenza exposure without risk of influenza-related complications.

In summary, there is an indication of considerable added benefit of baloxavir marboxil in comparison with the ACT of watchful waiting for adult and adolescent patients aged 12 years and above with influenza exposure without risk of influenza-related complications.

Research question 2: individuals aged 12 years and above with influenza exposure with risk of influenza-related complications

The company did not present any data for the assessment of the added benefit of baloxavir marboxil in adult and adolescent patients aged 12 years and above with risk of influenza-related complications. An added benefit of baloxavir marboxil in comparison with the ACT is thus not proven.

Table 3 shows a summary of probability and extent of the added benefit of baloxavir marboxil.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Baloxavir marboxil – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
1	Adult and adolescent patients aged 12 years and above with influenza exposure without risk of influenza-related complications	Watchful waiting	Indication of considerable added benefit[c]
2	Adult and adolescent patients aged 12 years and above with influenza exposure with risk of influenza-related complications	Antiviral therapy (oseltamivir or zanamivir)[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Official recommendations, epidemiological variability and the impact of the disease in different geographical regions and patient groups should be taken into account when using antiviral drugs for the post-exposure prophylaxis of influenza.
c. In the BLOCKSTONE study, all index patients received antiviral therapy. No data are available for the situation in which index patients do not receive antiviral therapy.

ACT: appropriate comparator; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of baloxavir marboxil in comparison with the ACT for PEP of influenza in adult and adolescent patients aged 12 years and above.

In its specification of the ACT, the G-BA differentiated between 2 patient groups in the approved therapeutic indication. This resulted in 2 research questions for the assessment; their subindications and ACTs are presented in Table 4.

Table 4: Research questions of the benefit assessment of baloxavir marboxil

Research question	Subindication	ACT[a]
1	Adult and adolescent patients aged 12 years and above with influenza exposure without risk of influenza-related complications	Watchful waiting
2	Adult and adolescent patients aged 12 years and above with influenza exposure with risk of influenza-related complications	Antiviral therapy (oseltamivir or zanamivir)[b]

a. Presentation of the respective ACT specified by the G-BA.
b. Official recommendations, epidemiological variability and the impact of the disease in different geographical regions and patient groups should be taken into account when using antiviral drugs for the post-exposure prophylaxis of influenza.

ACT: appropriate comparator; G-BA: Federal Joint Committee

The term "patient" includes all individuals with exposure to influenza. In the following, the term "individuals" is therefore used.

For easier presentation and better readability, the present benefit assessment uses the following terms for the research questions in the running text:

- Research question 1: individuals aged 12 years and above with influenza exposure without risk of influenza-related complications
- Research question 2: individuals aged 12 years and above with influenza exposure with risk of influenza-related complications

Research questions 1 and 2 of the present benefit assessment correspond to the patient groups a and b in the G-BA's specification of the ACT.

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used for the derivation of the added benefit. This corresponds to the inclusion criteria of the company for research question 1. The company did not describe any inclusion criteria for research question 2.

2.3 Research question 1: individuals aged 12 years and above with influenza exposure without risk of influenza-related complications

2.3.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on baloxavir marboxil (status: 22 November 2020)
- bibliographical literature search on baloxavir marboxil (last search on 22 November 2020)
- search in trial registries/trial results databases for studies on baloxavir marboxil (last search on 22 November 2020)
- search on the G-BA website for baloxavir marboxil (last search on 22 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on baloxavir marboxil (last search on 23 February 2021)

The check did not identify any additional relevant studies.

2.3.2 Studies included

The study listed in the following Table 5 was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: baloxavir marboxil vs. placebo

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication yes/no [citation])
1719T0834 (BLOCKSTONE[c])	Yes	Yes	No	No[d]	Yes [3,4]	Yes [5]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. In the following tables, the study is referred to with this abbreviated form.
d. Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without access to the CSR in Module 5 of the dossier.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

The study pool for the benefit assessment of baloxavir marboxil consists of the RCT 1719T0834 (hereinafter referred to as "BLOCKSTONE" study). This concurs with the company's study pool.

2.3.3 Study characteristics

Table 6 and Table 7 describe the study used for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: baloxavir marboxil vs. placebo

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
BLOCKSTONE	RCT, double-blind, parallel	Individuals who lived in the same household as an index patient[b] for ≥ 48 hours ▪ without influenza infection[c] in the investigator's assessment ▪ study inclusion within 24 hours after inclusion of the index patient	Baloxavir marboxil (N = 375) placebo (N = 377) Relevant subpopulation thereof[d]: baloxavir marboxil (n = 275) placebo (n = 274)	Screening: on the day of randomization Treatment: 1 day Observation: 14 days[e]	52 centres in Japan 11/2018–3/2019	Primary: proportion of patients with influenza confirmed by RT-PCR, fever and at least one respiratory symptom Secondary: morbidity, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes only include information on relevant available outcomes for this benefit assessment.
b. The following inclusion criteria apply to the index patients:
- positive rapid influenza diagnostic test by nasopharyngeal or throat swab
- informed consent to study participation within 48 hours after onset of symptoms (defined as rise in body temperature to ≥ 37.5°C)
- use of any anti-influenza drug (including baloxavir marboxil) after informed consent to study participation

c. Defined as: axillary body temperature < 37.0°C + no influenza like symptoms (cough, sore throat, headache, nasal congestion or discharge, feverishness or chills, muscle or joint pain, fatigue) on the day of screening; individuals with previous influenza during the 2018/2019 influenza season were excluded from study participation.
d. Patients aged 12 years and above without the following risks for influenza-related complications (according to CDC criteria): age ≥ 65 years, pregnancy or up to 2 weeks postpartum, residents of long-term care facilities, American Indians and Alaskan natives, chronic respiratory disease including COPD, cystic fibrosis and bronchial asthma, neurological conditions (e.g. epilepsy, stroke), and neurodevelopmental conditions, heart disease, blood disorders, endocrine disorders including diabetes mellitus, kidney disorders liver disorders, metabolic disorders, weakened immune system (including as a consequence of immunosuppressive therapy, cancer, HIV infection), BMI ≥ 40 kg/m², patients < 19 years of age who are receiving long-term acetylsalicylic acid therapy.
e. Follow-up observation of efficacy outcomes was 10 days. Outcomes of the category "side effects" were observed up to 14 days. All AEs were observed until resolution or until the condition became stable or chronic, but not longer than 28 days after study drug dosing. Treatment-related SAEs or liver function abnormalities were observed until resolution or the condition became stable or chronic.

AE: adverse event; BMI: body mass index; CDC: Centers for Disease Control and Prevention; COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event

Table 7: Characteristics of the intervention – RCT, direct comparison: baloxavir marboxil vs. placebo

Study	Intervention	Comparison
BLOCKSTONE	Baloxavir marboxil orally on day 1 ▪ 40 mg orally for < 80 kg body weight ▪ 80 mg orally for ≥ 80 kg body weight	Placebo orally on day 1
	Non-permitted pretreatment ▪ baloxavir marboxil, peramivir, laninamivir, oseltamivir, zanamivir or amantadine within 30 days prior to screening (including prophylaxis) ▪ treatment of a concomitant disease for systemic or nasal use (antipyretics or analgesics, corticosteroids, immunosuppressive agents) ▪ investigational drugs within 30 days or 5 half-lives prior to screening **Non-permitted concomitant treatment** ▪ antipyretics or analgesics[a] ▪ anti-influenza drugs (including herbal medicines)[a] ▪ corticosteroids ▪ immunosuppressive agents ▪ influenza vaccines ▪ investigational preparations	

a. The use of anti-influenza drugs and antipyretics/analgesics was permitted if influenza was diagnosed, influenza like symptoms or AEs occurred, and the investigator judged the use to be necessary.

AE: adverse event; RCT: randomized controlled trial

The BLOCKSTONE study is a double-blind RCT comparing baloxavir marboxil with placebo, conducted exclusively in Japan.

The study included only adults and children who had contact in their own household with a patient who had influenza (hereinafter referred to as “index patient”). The index patient had to have tested positive for the influenza virus by rapid test. The symptoms, defined as a first rise in body temperature to ≥ 37.5°C, must have started no more than 48 hours before signing the informed consent form. After study inclusion, the index patients received antiviral therapy. In addition, the index patient had to be the first individual in a household with influenza infection in the 2018/2019 influenza season. A total of 545 index patients were enrolled in the BLOCKSTONE study. About 90% of the index patients were younger than 20 years.

The individuals examined in the BLOCKSTONE study were those who had contact with the index patients and were thus exposed to the influenza virus. The individuals had lived in the same household as the index patient for 48 hours or more prior to informed consent. At enrolment, the individuals were not allowed to have influenza symptoms such as fever or cough. The informed consent of the individuals examined had to be provided within 24 hours from informed consent of the index patients. In addition, the individuals examined had to live with the index patients until at least day 10 of the study.

In the BLOCKSTONE study, individuals were randomly assigned to the 2 study arms. The stratification factors were time from onset of influenza virus infection of index patient to informed consent of individual (< 24 hours, ≥ 24 hours), treatment of index patient (baloxavir marboxil, other drug) and individual's age (< 12 years, ≥ 12 years). 375 individuals were randomized to the intervention arm and 377 to the comparator arm.

Baloxavir marboxil was administered in compliance with the SPC [6]. Individuals in the comparator arm received matching placebo.

Follow-up observation for efficacy outcomes was 10 days. This is considered to be sufficiently long in the present therapeutic indication, as the average infectivity period is 4 to 5 days after symptom onset and the average incubation period is 1 to 2 days [7]. Therefore, it is assumed that, if infection did occur during the selected observation period, the influenza infection would have become apparent in the individuals examined in the study. Nevertheless, a longer observation period for efficacy outcomes would be meaningful in principle in order to be able to draw conclusions about the course of the disease.

Primary outcome of the study was symptomatic influenza (fever and respiratory symptom) confirmed by RT-PCR. Further patient-relevant outcomes on morbidity and side effects were additionally recorded.

Study population of Asian family origin only

The BLOCKSTONE study is the only RCT conducted in the therapeutic indication of PEP. Only individuals of Asian family origin were included in this study. Thus, the target population in Germany is not adequately represented by the group of individuals examined in the BLOCKSTONE study. In the context of the approval, this aspect was addressed and not classified as a restriction for the approval of the therapeutic indication of PEP [8]. Overall, despite the lack of data on individuals of non-Asian family origin in the present therapeutic indication, it is also assumed that the effects observed in the Japanese study population of the BLOCKSTONE study can also be transferred with sufficient certainty to individuals of non-Asian family origin.

Relevant subpopulation for research question 1

According to the SPC, baloxavir marboxil is approved for individuals aged ≥ 12 years [6]. Individuals aged < 12 years were also included in the study, however. In addition, research question 1 of the present benefit assessment refers exclusively to individuals without risk of influenza-related complications. However, the study also included individuals with risk for influenza-related complications. Only results of the subpopulation aged ≥ 12 years and without risk of influenza-related complications are therefore relevant for research question 1. A total of 549 individuals correspond to the relevant subpopulation, of which 275 individuals in the intervention arm and 274 individuals in the comparator arm.

Implementation of the appropriate comparator therapy

The G-BA specified watchful waiting as ACT for research question 1 of the present benefit assessment.

The BLOCKSTONE study operationalized watchful waiting as a follow-up observation strategy. In addition, a placebo was administered in the comparator arm to ensure blinding. According to the study protocol, follow-up included daily entries on the presence and assessment of symptoms typical of influenza in an electronic diary using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe). The individuals also measured their axillary body temperature. All recordings were made in the morning and evening. In addition, according to the study protocol, one visit was scheduled on each of days 5 and 11, as well as one additional visit between days 1 and 10 if symptoms occurred. At these visits, a swab was taken for RT-PCR testing and a medical examination was performed. In case of influenza symptoms, appropriate therapy could be initiated.

In summary, the ACT was adequately implemented in the BLOCKSTONE study.

Patient characteristics

Table 8 shows the characteristics of individuals of the relevant subpopulation in the BLOCKSTONE study.

Table 8: Characteristics of the study population – RCT, direct comparison: baloxavir marboxil vs. placebo

Study **Characteristic** **Category**	**Baloxavir marboxil** **N[a] = 275**	**Placebo** **N[a] = 274**
BLOCKSTONE		
Age [years], mean (SD)	39 (9)	38 (9)
Sex [F/M], %	85/15	84/16
Family origin, n (%)		
Asian	275 (100)	274 (100)
Relation to index patient, n (%)		
Parent	245 (89.1)	240 (87.6)
Sibling	15 (5.5)	22 (8.0)
Child	3 (1.1)	3 (1.1)
Spouse	9 (3.3)	6 (2.2)
Other	3 (1.1)	3 (1.1)
Smoking status, n (%)		
Smoker	34 (12.4)	35 (12.8)
Never smoker	241 (87.6)	239 (87.2)
Influenza vaccination within the previous 6 months, n (%)		
Yes	99 (36.0)	90 (32.8)
No	176 (64.0)	184 (67.2)
Time from onset of influenza infection of index patient to informed consent of individual, n (%)		
< 24 h	199 (72.4)	199 (72.6)
≥ 24 h	76 (27.6)	75 (27.4)
Influenza test result at baseline, n (%)		
Negative	254 (92.4)	252 (92.0)
Positive	21 (7.6)[b]	22 (8.0)[b]
A/H1N1pdm	1 (0.4)	7 (2.6)
A/H3NX	14 (5.1)	9 (3.3)
A/ND	6 (2.2)	6 (2.2)
Treatment discontinuation, n (%)	0 (0)	1 (0.4)[c]
Study discontinuation, n (%)	ND	ND

a. Number of randomized individuals.
b. Institute's calculation; according to information provided by the company in Module 4B, 25 individuals in the intervention arm and 23 individuals in the comparator arm were excluded from the analysis in the context of a sensitivity analysis without confirmation of the influenza infection by laboratory diagnostics at baseline.
c. Data from Module 4 B; discrepancy with data in the FDA review [9].

AE: adverse event; F: female; FDA: Food and Drug Administration; M: male; n: number of individuals in the category; N: number of randomized (or included) individuals; ND: no data; RCT: randomized controlled trial; SD: standard deviation

The demographic characteristics of the individuals in the relevant subpopulation were sufficiently comparable.

The mean age of the individuals was about 38 years, and the majority were female. All individuals were of Asian family origin and about 90% were parents of the index patients. About 1 third of the individuals investigated had received an influenza vaccination in the 6 months before the start of the study.

In a small proportion of individuals (< 10%), the RT-PCR test for influenza was already positive at baseline. According to the SPC, these are included in the therapeutic indication, however [6]. As a rule, no confirmation by laboratory diagnostics is carried out before treatment with an antiviral drug.

In over 70% of the individuals, informed consent was obtained within 24 hours from the onset of the index patient's influenza infection.

Risk of bias across outcomes (study level)

Table 9 shows the risk of bias across outcomes (risk of bias at study level).

Table 9: Risk of bias across outcomes (study level) – RCT, direct comparison: baloxavir marboxil vs. placebo

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
BLOCKSTONE	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes for the BLOCKSTONE study was rated as low. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company described that the relevant subpopulation of the BLOCKSTONE study included both female and male patients whose age-specific weight was comparable to that of the population in Germany. According to the company, the vaccination rate in the relevant subpopulation was slightly higher than in the population in Germany in the 2014/2015 influenza season, but the number of smokers was slightly lower than in Germany in 2017. The company further stated that transferability was given with regard to the virus types or virus subtypes prevalent in the 2018/2019 season.

Only individuals of Asian family origin were included in the BLOCKSTONE study. However, the company assumed that it was possible to demonstrate the transferability of the efficacy, which it considered clinically relevant, from Asian to non-Asian patients in the therapeutic indication of PEP. For this purpose, it designated a holistic exposure matching approach that considers criteria that are not dependent on family origin (e.g. mechanism of action as well as pharmacokinetic parameters such as maximum plasma concentration [C_{max}] or the plasma concentration of baloxavir marboxil after 24, 72 or 240 hours [C_{24}, C_{72} or C_{240}]). To check the transferability of the results of the BLOCKSTONE study to non-Asian individuals, the company used the studies CAPSTONE-1 and CAPSTONE-2. Both studies were conducted to investigate the efficacy of treatment with baloxavir marboxil in the presence of influenza infection and included patients of Asian family origin as well as patients of non-Asian family origin. According to the company, the comparison of C_{24}, C_{72} and C_{240} in non-Asian patients aged ≥ 12 years with those in Asian patients aged < 12 years after administration of 40 mg baloxavir marboxil in the studies CAPSTONE-1 and CAPSTONE-2 showed that this dosage was effective despite a slightly lower median C_{24} value in the Asian patients aged < 12 years. In addition, the median exposure ranges $C_{24,}$ C_{72} and C_{240} largely overlapped. From this, the company concluded that the weight-based dosing regimen for individuals of non-Asian family origin was appropriate for PEP and that the results from individuals of Asian family origin could be transferred to those of non-Asian family origin.

Overall, according to the company, the study population of the BLOCKSTONE study is comparable to the patient population in the German health care context and the results are therefore transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3.4 Results on added benefit

2.3.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - symptomatic influenza
- Health-related quality of life
- Side effects
  - SAEs
  - discontinuation due to AEs

- further specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier (Module 4 B).

Table 10 shows for which outcomes data were available in the study included.

Table 10: Matrix of outcomes – RCT, direct comparison: baloxavir marboxil vs. placebo

Study	Outcomes					
	All-cause mortality	Symptomatic influenza infection[a]	Health-related quality of life	SAEs	Discontinuation due to AEs[c]	Specific AEs
BLOCKSTONE	Yes	Yes	No[b]	Yes	Yes	No[d]

a. Operationalized as fever ≥ 37.5 C or at least one other influenza symptom (cough, sore throat, nasal discharge/nasal congestion, headache, chills, muscle or joint pain, or fatigue with a severity of "2 (moderate)" or "3 (severe)", additionally positive RT-PCR test.
b. Outcome not recorded.
c. Insufficient efficacy (such as the occurrence of an influenza virus infection) or a change in influenza symptoms after the occurrence of an influenza virus infection were not documented as AEs unless classified as SAEs.
d. No specific AEs were identified.

AE: adverse event; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event

Morbidity

Symptomatic influenza infection

For the outcome "influenza infection", the company provided the proportion of individuals for the following operationalizations:

- symptomatic influenza infection with fever ≥ 37.5°C and ≥ 1 respiratory symptom (cough or nasal discharge/nasal congestion) with a severity of "2 = moderate" or "3 = severe", and additionally a positive RT-PCR test between day 1 and day 10 (primary outcome of the BLOCKSTONE study).
- symptomatic influenza infection with fever ≥ 37.5 C or ≥ 1 other influenza symptom (cough, sore throat, nasal discharge/nasal congestion, headache, chills, muscle or joint pain, or fatigue with a severity of "2 = moderate" or "3 = severe", and additionally a positive RT-PCR test between day 1 and day 10.

- influenza infection detected by positive RT-PCR test between day 1 and day 11, regardless of symptoms

Symptomatic influenza infection, operationalized as fever or ≥ 1 other influenza symptom and additionally a positive RT-PCR test, was used for the present benefit assessment. This operationalization includes a larger number of possible influenza symptoms and thus better represents the clinically variable picture of influenza than the primary outcome of the study, operationalized as fever and ≥ 1 respiratory symptom and additionally a positive RT-PCR test. The results of the primary outcome are not presented in the present benefit assessment. However, they are comparable to those of the operationalization used in the benefit assessment.

In addition to the proportion of individuals with event, the company also presented event time analyses for the operationalizations for symptomatic influenza as supplementary information. These were not used, however, because in the present therapeutic indication it is of interest how many individuals get an influenza infection after PEP and not the time when the influenza infection occurs. This concurs with the company's assessment.

In addition, the influenza infection detected by RT-PCR test, regardless of symptoms, is presented as supplementary information as this operationalization provides information beyond symptomatic influenza infection for the present therapeutic indication of PEP of influenza.

2.3.4.2 Risk of bias

Table 11 describes the risk of bias for the results of the relevant outcomes.

Table 11: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: baloxavir marboxil vs. placebo

Study	Study level	Outcomes					
		All-cause mortality	Symptomatic influenza infection[a]	Health-related quality of life	SAEs[b]	Discontinuation due to AEs[c]	Specific AEs
BLOCKSTONE	L	L	L	-[d]	L	L	-[e]

a. Operationalized as fever ≥ 37.5 C or at least one other influenza symptom (cough, sore throat, nasal discharge/nasal congestion, headache, chills, muscle or joint pain, or fatigue with a severity of "2 (moderate)" or "3 (severe)", additionally positive RT-PCR test.
b. The outcome "SAEs" may in principle include events that can potentially be attributed to the underlying disease. However, the only SAE that occurred was the PT psychosis.
c. Insufficient efficacy (such as the occurrence of an influenza virus infection) or a change in influenza symptoms after the occurrence of an influenza virus infection were not documented as AEs unless classified as SAEs. However, the only SAE that occurred was the PT psychosis.
d. Outcome not recorded.
e. No specific AEs were identified.

AE: adverse event; L: low; PT: Preferred Term, RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event

The outcome-specific risk of bias for all outcomes used in the dossier assessment was rated as low. This concurs with the company's assessment.

2.3.4.3 Results

Table 12 summarizes the results of the comparison of baloxavir marboxil with placebo in individuals aged 12 years and above with influenza exposure without risk of influenza-related complications. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

Table 12: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: baloxavir marboxil vs. placebo

Study Outcome category Outcome	Baloxavir marboxil		Placebo		Baloxavir marboxil vs. placebo
	N	Individuals with event n (%)	N	Individuals with event n (%)	RR[a] [95% CI]; p-value
BLOCKSTONE					
Mortality					
All-cause mortality	275	0 (0)	274	0 (0)	–
Morbidity					
Symptomatic influenza infection[b, c]	275	10 (3.6)	274	59 (21.5)	0.17 [0.09; 0.32]; < 0.001
Positive RT-PCR test for influenza regardless of symptoms (supplementary information)	*275*	*27 (9.8)*	*274*	*81 (29.6)*	*0.33 [0.22; 0.49]; < 0.001*
Side effects					
AEs[d] (supplementary information)	275	54 (19.6)	274	49 (17.9)	–
SAEs	275	0 (0)	274	1 (0.4)	–[e]
Discontinuation due to AEs	275	0 (0)	274	1 (0.4)	–[e]

a. RR with CI and p-value: modified Poisson regression adjusted for time from onset of influenza virus infection of index patient to informed consent of individual, treatment of index patient (baloxavir marboxil, other medication) at baseline.
b. Operationalized as fever ≥ 37.5 C or at least one other influenza symptom (cough, sore throat, nasal discharge/nasal congestion, headache, chills, muscle or joint pain, or fatigue with a severity of "2 (moderate)" or "3 (severe)", additionally positive RT-PCR test.
c. There is no information available on the frequency of the individual symptoms.
d. Insufficient efficacy (such as the occurrence of an influenza virus infection) or a change in influenza symptoms after the occurrence of an influenza virus infection were not documented as AEs unless classified as serious.
e. No presentation of effect estimation with CI and p-value, as these are not informative.

AE: adverse event; CI: confidence interval; n: number of individuals with (at least one) event; N: number of analysed individuals; RCT: randomized controlled trial; RR: relative risk; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event

Based on the available data, no more than indications, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

No death occurred in the BLOCKSTONE study. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with watchful waiting; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Symptomatic influenza infection

A statistically significant difference in favour of baloxavir marboxil in comparison with placebo was shown for the outcome "symptomatic influenza infection". This positive effect was also shown in the proportion of individuals with a positive RT-PCR test for influenza regardless of symptoms, presented as supplementary information. There was an indication of an added benefit of baloxavir marboxil in comparison with watchful waiting.

This concurs with the assessment of the company, which used an additional operationalization of the category of morbidity, however. In addition, the company used the proportion of individuals with a positive RT-PCR test for influenza regardless of symptoms as a separate outcome.

Health-related quality of life

No outcomes in the outcome category "health-related quality of life" were recorded in the BLOCKSTONE study. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with watchful waiting in this outcome category; an added benefit is therefore not proven.

This concurs with the assessment of the company, which claimed no added benefit for this outcome category.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between baloxavir marboxil and placebo for either of the outcomes "SAEs" and "discontinuation due to AEs". This resulted in no hint of greater or lesser harm from baloxavir marboxil in comparison with watchful waiting; an added benefit is therefore not proven.

This concurs with the assessment of the company, which used additional outcomes of the category of side effects, however.

2.3.4.4 Subgroups and other effect modifiers

The following subgroups were considered in the present benefit assessment:

- sex (female, male)
- time from onset of influenza virus infection of index patient to informed consent of the patient (< 24 hours, ≥ 24 hours)
- vaccination status of the individual (yes, no)

No analyses are available for the relevant subpopulation on the subgroup characteristic of age, which is also relevant in principle.

Interaction tests were performed when at least 10 individuals per subgroup were included in the analysis. Moreover, for binary data, there had to be 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are only presented if there is a statistically significant and relevant effect in at least one subgroup.

Apart from the subgroup characteristic of age, the company presented subgroup analyses for the outcome "symptomatic influenza infection" for all characteristics relevant for the present benefit assessment. The company did not provide any subgroup analyses for the outcomes "mortality", "SAEs" and "discontinuation due to AEs". The approach of the company is adequate, as there were fewer than 10 events for these outcomes.

For the outcome "symptomatic influenza infection", no relevant effect modification by the characteristics considered in the benefit assessment was identified according to the methods described.

This concurs with the company's assessment.

2.3.5 Probability and extent of added benefit

Probability and extent of the added benefit at outcome level are derived below, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on the added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.3.5.1 Assessment of the added benefit at outcome level

The extent of the respective added benefit at outcome level is estimated from the results presented in Section 2.3.4 (see Table 13).

Determination of the outcome category for symptom outcomes

It cannot be inferred from the dossier for all outcomes considered in the present benefit assessment whether they are serious/severe or non-serious/non-severe. The classification of these outcomes is justified below.

Symptomatic influenza infection

Based on the population considered (individuals aged 12 years and above with influenza exposure without risk of influenza-related complications), it is assumed that the events included in the outcome "symptomatic influenza infection" were rather non-serious/non-severe. Therefore, the outcome was assigned to the outcome category of non-serious/non-severe symptoms/late complications.

The company did not provide any information on the assessment of the severity of the events that occurred.

The company did not make an assignment to the outcome category.

Table 13: Extent of added benefit at outcome level: baloxavir marboxil vs. placebo

Outcome category **Outcome**	**Baloxavir marboxil vs. placebo** **Proportion of events (%)** **RR [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Symptomatic influenza infection	3.6% vs. 21.5% RR: 0.17 [0.09; 0.32]; p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications CI_u < 0.80 added benefit, extent: "considerable"
Health-related quality of life		
–	Outcomes from this category were not recorded	Lesser benefit/added benefit not proven
Side effects		
SAEs	0% vs. 0.4% -[c]	Lesser benefit/added benefit not proven
Discontinuation due to AEs	0% vs. 0.4% -[c]	Lesser benefit/added benefit not proven

a. Probability provided if there is a statistically significant and relevant effect.
b. Depending on the outcome category, estimations of effect size are made with different limits based on the upper limit of the confidence interval (CI_u).
c. No presentation of effect estimation with CI and p-value, as these are not informative.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; RR: relative risk; SAE: serious adverse event

2.3.5.2 Overall conclusion on added benefit

Table 14 summarizes the results considered in the overall conclusion on the extent of the added benefit.

Table 14: Positive and negative effects from the assessment of baloxavir marboxil in comparison with watchful waiting

Positive effects	Negative effects
Non-serious/non-severe symptoms/late complications ▪ Symptomatic influenza infection: indication of an added benefit – extent: "considerable"	–
Outcomes from the category of health-related quality of life were not recorded.	

In the overall picture, there is exclusively one positive effect of considerable extent for the outcome "symptomatic influenza infection" for individuals aged 12 years and above with influenza exposure without risk of influenza-related complications.

In summary, there is an indication of considerable added benefit of baloxavir marboxil in comparison with the ACT of watchful waiting for adult and adolescent patients aged 12 years and above with influenza exposure without risk of influenza-related complications.

The assessment described above concurs with that of the company insofar as the company also derived an indication of considerable added benefit.

2.4 Research question 2: individuals aged 12 years and above with influenza exposure with risk of influenza-related complications

2.4.1 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company in the dossier:

- study list on baloxavir marboxil (status: 22 November 2020)
- bibliographical literature search on baloxavir marboxil (last search on 22 November 2020)
- search in trial registries/trial results databases for studies on baloxavir marboxil (last search on 22 November 2020)
- search on the G-BA website for baloxavir marboxil (last search on 22 November 2020)

To check the completeness of the study pool:

- search in trial registries for studies on baloxavir marboxil (last search on 23 February 2021)

Concurring with the company, the check identified no relevant study.

The company overall did not formulate inclusion criteria for research question 2.

2.4.2 Results on added benefit

The company did not present any data for the assessment of the added benefit of baloxavir marboxil in comparison with the ACT for adult and adolescent patients aged 12 years and above with influenza exposure with risk of influenza-related complications. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with the ACT. An added benefit is therefore not proven.

This concurs with the company's assessment.

2.4.3 Probability and extent of added benefit

The company did not present any data for the assessment of the added benefit of baloxavir marboxil in adult and adolescent patients aged 12 years and above with risk of influenza-related complications. An added benefit of baloxavir marboxil in comparison with the ACT is thus not proven.

2.5 Probability and extent of added benefit – summary

Table 15 summarizes the result of the assessment of the added benefit of baloxavir marboxil in comparison with the ACT.

Table 15: Baloxavir marboxil – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult and adolescent patients aged 12 years and above with influenza exposure without risk of influenza-related complications	Watchful waiting	Indication of considerable added benefit[c]
2	Adult and adolescent patients aged 12 years and above with influenza exposure with risk of influenza-related complications	Antiviral therapy (oseltamivir or zanamivir)[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. Official recommendations, epidemiological variability and the impact of the disease in different geographical regions and patient groups should be taken into account when using antiviral drugs for the post-exposure prophylaxis of influenza.
c. In the BLOCKSTONE study, all index patients received antiviral therapy. No data are available for the situation in which index patients do not receive antiviral therapy.

ACT: appropriate comparator; G-BA: Federal Joint Committee

The approach for the derivation of an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-22.html.