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Baloxavir marboxil (influenza) –

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

Extract

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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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GCP	good clinical practice
EQ-5D	European Quality of Life-5 Dimensions
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
ITTI	intention to treat infected
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
VAS	visual analogue scale

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) in patients aged 12 years and above with uncomplicated influenza.

The G-BA differentiated between 2 patient groups in its specification of the ACT in the approved therapeutic indication. This resulted in 2 research questions for the assessment; their respective subindication and ACT specified by G-BA are presented in Table 2.

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

Research question	Subindication	ACT[a]
1	Patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications	Symptomatic therapy (antipyretics, antiphlogistics, analgesics)[b]
2	Patients aged 12 years and above with uncomplicated influenza if there is an increased risk of a severe course of the disease	Antiviral therapy **(oseltamivir** or zanamivir)[b, c]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that supportive measures (e.g. sufficient hydration) as well as concomitant symptomatic therapy (e.g. antipyretics, antiphlogistics, analgesics) are carried out in both study arms.
c. 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 treatment of influenza.

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

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

- Research question 1: patients without risk of influenza-related complications
- Research question 2: patients with an increased risk of a severe course of the disease

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 on the ACT. For research question 2, the company chose oseltamivir from the options mentioned by the G-BA.

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.

Research question 1: patients without risk of influenza-related complications

Study pool of the company

The company used the 2 RCTs JapicCTI-153090 und CAPSTONE-1 for research question 1. Both studies investigated patients who had no risk factors for influenza-related complications. In addition, patients with a severe course of the disease at enrolment were excluded.

The JapicCTI-153090 study is a double-blind RCT comparing baloxavir marboxil at doses of 10 mg, 20 mg or 40 mg against placebo. The study included patients aged ≥ 20 to < 65 years with influenza confirmed by antigen test. In addition, the patients had to have influenza symptoms. Only patients with a body weight < 80 kg who received 40 mg baloxavir marboxil were treated in compliance with the Summary of Product Characteristics (SPC). Accordingly, the company analysed this subpopulation for the comparison of baloxavir marboxil 40 mg against placebo.

The CAPSTONE-1 study is a double-blind RCT on the comparison of baloxavir marboxil, oseltamivir and placebo. The oseltamivir arm is not relevant for research question 1 of the benefit assessment and is therefore not considered further. The study included patients aged ≥ 12 to ≤ 64 years with influenza confirmed by symptomatic diagnosis.

Appropriate comparator therapy not implemented in the studies JapicCTI-153090 and CAPSTONE-1

The studies JapicCTI-153090 and CAPSTONE-1 did not allow the use of symptomatic therapy with the exception of paracetamol. This drug was only allowed to be taken in cases where influenza symptoms, such as fever, headache or muscle pain, were so severe that the patient needed "rescue therapy".

In the JapicCTI-153090 study, in the subpopulation analysed by the company, 77% of patients in the baloxavir marboxil arm (40 mg) and 78% in the placebo arm took paracetamol at least once during the course of the study. Information on the frequency of use is missing. In the CAPSTONE-1 study, the proportion of patients in the population who tested positive for influenza analysed by the company was 6.6% in the baloxavir marboxil arm and 4.8% in the placebo arm. In both studies, it is unclear overall how often how many patients would have made use of symptomatic therapy to relieve symptoms without the restriction described in the

study protocols. Due to the restriction in the use of symptomatic therapy mandated by the study protocol, both studies do not allow to draw conclusions on the added benefit for patient-relevant outcomes regarding influenza symptoms and health status.

Thus, there are no suitable data for the assessment of the added benefit of baloxavir marboxil in comparison with the ACT. This resulted in no hint of an added benefit of baloxavir marboxil in comparison with the ACT; an added benefit is therefore not proven.

Research question 2: patients with an increased risk of a severe course of the disease

Study pool and study characteristics

The study pool for the benefit assessment of baloxavir marboxil in patients with an increased risk of a severe course of the disease consists of the CAPSTONE-2 study. The study is a double-blind RCT on the comparison of baloxavir marboxil, oseltamivir and placebo. The placebo arm is not relevant for the present benefit assessment. The study included patients aged ≥ 12 years with influenza confirmed by symptomatic diagnosis. Patients had to have at least one risk factor for influenza-related complications. Patients with a severe course of the disease at enrolment were excluded.

Baloxavir marboxil and oseltamivir were administered without relevant deviations from the SPCs.

The primary outcome of the study was the time to alleviation of influenza symptoms (taking into account the change in pre-existing symptoms). Further patient-relevant outcomes were outcomes on symptoms, health status and adverse events (AEs).

Analysis populations of the CAPSTONE-2 study

The company used different analysis populations for outcomes on morbidity and outcomes on side effects and mortality (deaths were recorded as part of the AE recording).

For the assessment of the morbidity outcomes, the company limited the total population to patients who received the study medication, and who had a positive influenza test confirmed by reverse transcriptase polymerase chain reaction (RT-PCR), and who were included in centres that provide treatment in accordance with good clinical practice ("intention to treat infected [ITTI] population"; n = 388 in the baloxavir marboxil arm and n = 389 in the oseltamivir arm). For the outcomes on side effects and mortality, the company analysed the patients who had received at least one dose of the study medication (safety population; n = 730 in the baloxavir marboxil arm and n = 721 in the oseltamivir arm).

The approach of the company to use the ITTI population for the assessment of the outcome of the category of morbidity is not adequate. The analysis of the ITTI population is relevant for the exclusive assessment of efficacy in the context of the approval; for the early benefit assessment, however, it is of interest how patients are treated in everyday health care. The analysis of the total population (ITT) without confirmed influenza diagnosis generally reflects

the conditions in health care because the diagnosis and subsequent treatment decision for antiviral treatment in clinical practice is generally not dependent on the laboratory diagnostic evidence of influenza. The present benefit assessment therefore uses the total population of the CAPSTONE-2 study for the assessment of all outcome categories, i.e. including the outcomes on morbidity. Analyses of the ITTI population with influenza confirmed by RT-PCR are additionally considered.

Risk of bias

The risk of bias across outcomes was rated as low for CAPSTONE-2 study. The risk of bias of the results for the included outcomes "all-cause mortality", "SAEs" and "discontinuation due to AEs" was rated as low in each case. For outcomes in the outcome category of morbidity, no analyses are available for the total population relevant to the assessment.

Results

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for this outcome; an added benefit is therefore not proven.

Morbidity

Influenza symptoms, health status (measured with the European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS], influenza-typical complications

No results for the relevant analysis population are available for the assessment of the added benefit regarding influenza symptoms, health status (EQ-5D VAS) and influenza-typical complications. In the ITTI population considered as supplementary information, there was no statistically significant difference between the treatment groups for any of the outcomes. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant to the assessment. Overall, this results in no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for the outcomes "influenza symptoms", "health status" (EQ-5D VAS) and "influenza-typical complications"; an added benefit is therefore not proven.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the CAPSTONE-2 study.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment arms 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 oseltamivir for either of these outcomes; greater or lesser harm is therefore not proven.

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

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:

Research question 1: patients without risk of influenza-related complications

As the company did not provide any suitable data for the assessment of the added benefit of baloxavir marboxil in comparison with the ACT of symptomatic therapy (antipyretics, antiphlogistics, analgesics) in patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications, an added benefit of baloxavir marboxil for these patients is not proven.

Research question 2: patients with an increased risk of a severe course of the disease

The CAPSTONE-2 study showed no positive or negative effects for patients with an increased risk of a severe course of the disease in the population with influenza confirmed by symptomatic diagnosis relevant for the benefit assessment, irrespective of laboratory diagnostic evidence. No results are available for the relevant population for morbidity outcomes (influenza symptoms, health status and influenza-typical complications). There were no statistically significant differences between the treatment groups for any of these 3 outcomes in the population of patients who tested positive for influenza (confirmed by RT-PCR). Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population. Therefore, it is not to be expected that the consideration of the relevant analysis population would produce a different result in terms of statistical significance.

In summary, there is no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for patients aged 12 years and above with uncomplicated influenza if there is an increased risk of a severe course of the disease.

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

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications	Symptomatic therapy (antipyretics, antiphlogistics, analgesics)[b]	Added benefit not proven
Patients aged 12 years and above with uncomplicated influenza if there is an increased risk of a severe course of the disease	Antiviral therapy **(oseltamivir** or zanamivir)[b, c]	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. It is assumed that supportive measures (e.g. sufficient hydration) as well as concomitant symptomatic therapy (e.g. antipyretics, antiphlogistics, analgesics) are carried out in both study arms. c. 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 treatment of influenza. ACT: appropriate comparator therapy; 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 in patients aged 12 years and above with uncomplicated influenza.

The G-BA differentiated between 2 patient groups in its specification of the ACT in the approved therapeutic indication. This resulted in 2 research questions for the assessment; their respective subindication and ACT specified by G-BA are presented in Table 2.

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

Research question	Subindication	ACT[a]
1	Patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications	Symptomatic therapy (antipyretics, antiphlogistics, analgesics)[b]
2	Patients aged 12 years and above with uncomplicated influenza if there is an increased risk of a severe course of the disease	Antiviral therapy **(oseltamivir** or zanamivir)[b, c]

a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**.
b. It is assumed that supportive measures (e.g. sufficient hydration) as well as concomitant symptomatic therapy (e.g. antipyretics, antiphlogistics, analgesics) are carried out in both study arms.
c. 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 treatment of influenza.

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

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

- Research question 1: patients without risk of influenza-related complications
- Research question 2: patients with an increased risk of a severe course of the disease

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 on the ACT. For research question 2, the company chose oseltamivir from the options mentioned by the G-BA.

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 concurs with the company's inclusion criteria.

2.3 Research question 1: patients 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)

No relevant study was identified from the check.

Study pool of the company

With the steps of information retrieval mentioned, the company identified the studies JapicCTI-153090 [3-5] and CAPSTONE-1 [4,6,7], which it considered relevant to research question 1.

The data presented by the company are not suitable for deriving conclusions on the added benefit of baloxavir marboxil in comparison with the ACT in patients without risk of influenza-related complications, as symptomatic therapy was not sufficiently implemented in either of the 2 studies. This is justified below. At first, the 2 studies included by the company are described.

Description of the studies included by the company

Study JapicCTI-153090

The JapicCTI-153090 study is a double-blind RCT comparing baloxavir marboxil at doses of 10 mg, 20 mg or 40 mg against placebo. The study included patients aged ≥ 20 to < 65 years with influenza confirmed by antigen test. In addition, patients had to have fever (defined as axillary temperature ≥ 38ºC) and at least one general symptom (headache, fever or chills, muscle or joint pain, fatigue) and one respiratory symptom typical of influenza (cough, sore throat, nasal congestion). The patients were not allowed to have risk factors for influenza-related complications. In addition, patients with a severe course of the disease at enrolment were excluded. A total of 400 patients were assigned in a 1:1:1:1 ratio to the 4 study arms. Randomization was stratified by symptom total score (≤ 11, ≥ 12) and smoking status (smoker, non-smoker).

Only patients with a body weight < 80 kg who received 40 mg baloxavir marboxil were treated in compliance with the SPC [8]. Accordingly, the company analysed this subpopulation for the comparison of baloxavir marboxil 40 mg (n = 90) against placebo (n = 94). Symptomatic therapy was not allowed except for the use of paracetamol if the symptoms were so severe that the patient needed "rescue therapy". The patients documented their use of paracetamol in electronic patient diaries.

The study duration was 22 days. The patients recorded their symptoms in electronic patient diaries. The severity of influenza symptoms (cough, sore throat, nasal congestion, headache,

fever or chills, muscle or joint pain, fatigue) was assessed using a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

The primary outcome of the study was the time to alleviation of influenza symptoms. Further patient-relevant outcomes were outcomes on symptoms, health status and AEs.

Further information on the characteristics of the JapicCTI-153090 study can be found in Appendix A of the full dossier assessment.

Study CAPSTONE-1

The CAPSTONE-1 study is a double-blind RCT on the comparison of baloxavir marboxil, oseltamivir and placebo. The study included patients aged ≥ 12 to ≤ 64 years with influenza confirmed by symptomatic diagnosis. The definition and recording of symptoms by means of an electronic diary was analogous to the JapicCTI-153090 study. The included patients were not allowed to have any risk factors for influenza-related complications. In addition, patients with a severe course of the disease at enrolment were excluded. A total of 1436 patients were randomly assigned to the 3 study arms of baloxavir marboxil (N = 612), oseltamivir (N = 514) and placebo (N = 310). Patients aged 20 to 64 years were assigned to treatment with baloxavir marboxil, oseltamivir or placebo in a 2:2:1 ratio; patients aged 12 to 19 years were assigned only to treatment with baloxavir marboxil or placebo in a 2:1 ratio. In both age groups, randomization was stratified by body weight (< 80 kg, ≥ 80 kg), region (Japan/Asia, rest of the world) and symptom total score (≤ 11, ≥ 12). The oseltamivir arm is not relevant for the assessment in research question 1 of the benefit assessment and is therefore not considered further.

Baloxavir marboxil was administered at weight-dependent doses of 40 mg and 80 mg, which was in compliance with the SPC [8]. As in the JapicCTI-153090 study symptomatic therapy, except for the use of paracetamol, was only allowed if the symptoms were so severe that the patient needed “rescue therapy”. The patients documented their use of paracetamol in electronic patient diaries.

The primary outcome of the study was the time to alleviation of influenza symptoms. Further patient-relevant outcomes were outcomes on symptoms, health status and AEs.

The study duration was 22 days.

The company analysed the total study population, limited to the patients who had received at least one dose of the study medication (safety population), for the assessment of side effects and mortality (deaths were recorded as part of the AE recording). For the assessment of the morbidity outcomes, the company limited the total population to patients who received the study medication, and who had a positive influenza test confirmed by RT-PCR (ITTI population).

Further information on the characteristics of the CAPSTONE-1 study can be found in Appendix A of the full dossier assessment.

Appropriate comparator therapy not implemented in the studies JapicCTI-153090 and CAPSTONE-1

The G-BA specified symptomatic therapy (antipyretics, antiphlogistics, analgesics) as the ACT for patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications. It is assumed that supportive measures (e.g. sufficient hydration) as well as concomitant symptomatic therapy (e.g. antipyretics, antiphlogistics, analgesics) were carried out in both study arms. In the studies JapicCTI-153090 and CAPSTONE-1, the use of antipyretics and analgesics, with the exception of paracetamol, was not allowed in either the intervention arm or the placebo arm. In addition, other symptomatic therapies such as antitussives and expectorants or combination cold preparations were not allowed in either study. The only concomitant symptomatic treatment allowed was paracetamol, which could be taken in cases where influenza symptoms, such as fever, headache or muscle pain, were so severe that the patient needed "rescue therapy". A maximum dose of paracetamol of 1500 mg/day was allowed in the JapicCTI-153090 study and of 3000 mg/day in the CAPSTONE-1 study. According to the SPC, a dose of up to 4000 mg/day is permitted [9].

In the JapicCTI-153090 study, in the subpopulation analysed by the company, 77% of patients in the baloxavir marboxil arm (40 mg) and 78% in the placebo arm took paracetamol at least once during the course of the study. Information on the frequency of use is missing. In the CAPSTONE-1 study, the proportion of patients in the ITTI population was 6.6% in the baloxavir marboxil arm and 4.8% in the placebo arm. Data on paracetamol use in the total population of the CAPSTONE-1 study are not available. The company did not give reasons for the extreme differences between the studies JapicCTI-153090 and CAPSTONE-1 in the use of paracetamol. Regardless of this, in both studies, it is unclear overall how often how many patients would have made use of symptomatic therapy to relieve symptoms without the restriction described in the study protocols. Due to the restriction in the use of symptomatic therapy mandated by the study protocol, both studies do not allow to draw conclusions on the added benefit for patient-relevant outcomes regarding influenza symptoms (headache, fever or chills, muscle or joint pain, fatigue, cough, sore throat, nasal congestion) and health status.

Due to the lack of implementation of the ACT, the studies JapicCTI-153090 and CAPSTONE-1 are therefore overall not suitable for the assessment of the added benefit of baloxavir marboxil in patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications.

2.3.2 Results on added benefit

The company did not provide any suitable data for the assessment of the added benefit of baloxavir marboxil in comparison with the ACT in patients aged 12 years and above with uncomplicated influenza without 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.

2.3.3 Probability and extent of added benefit

As the company did not provide any suitable data for the assessment of the added benefit of baloxavir marboxil in comparison with the ACT of symptomatic therapy (antipyretics, antiphlogistics, analgesics) in patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications, an added benefit of baloxavir marboxil for these patients is not proven.

This assessment deviates from that of the company, which derived proof of considerable added benefit on the basis of the meta-analytical summary of the RCTs JapicCTI-153090 and CAPSTONE-1.

2.4 Research question 2: patients with an increased risk of a severe course of the disease

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)

The check did not identify any additional relevant studies.

2.4.1.1 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. oseltamivir, patients with an increased risk of a severe course of the disease

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 and other sources[c] (yes/no [citation])
1602T0832 (CAPSTONE-2[d])	Yes	Yes	No	No[e]	Yes [10,11]	Yes [12,13]

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. Other sources: documents from the search on the G-BA website and other publicly available sources.
d. In the following tables, the study is referred to with this abbreviated form.
e. 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 in the present research question in patients aged 12 years and above with uncomplicated influenza with an increased risk of a severe course of the disease consists of the RCT CAPSTONE-2 and corresponds to that of the company.

2.4.1.2 Study characteristics

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

Table 6: Characteristics of the studies included – RCT, direct comparison: baloxavir marboxil vs. oseltamivir, patients with an increased risk of a severe course of the disease (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
CAPSTONE-2	RCT, double-blind, parallel	▪ Patients aged ≥ 12 years with influenza confirmed by symptomatic diagnosis[b] ▪ without severe course of the disease[c] ▪ with a high risk[d] of influenza-related complications ▪ study inclusion ≤ 48 h after symptom onset[e]	Baloxavir marboxil (N = 730) oseltamivir (N = 725) placebo (N = 729)[f] Subpopulation on morbidity outcomes analysed by the company[g]: baloxavir marboxil (n = 388) oseltamivir (n = 389)	Screening: on the day of randomization Treatment: 5 days Observation: until day 14 (symptoms) or until day 22 (health status) and day 35 (AEs)	551 centres in: Australia, Belgium, Germany, Hungary, Japan, Latvia, New Zealand, Philippines, Poland, Romania, South Africa, South Korea, Spain, USA 1/2017–4/2018	Primary: time to alleviation of influenza symptoms (taking into account the change in pre-existing symptoms) Secondary: symptoms, health status, 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. Diagnosis of influenza confirmed by all of the following:
- fever ≥ 38°C (axillary) during the predose examination or > 4 hours after dosing of an antipyretic if this was taken
- at least one each of the following general and respiratory symptoms associated with influenza (excluding chronic symptoms that existed in the 30 days prior to the influenza episode) with a severity of moderate or greater:
  - general symptoms: headache, fever or chills, muscle or joint pain, fatigue
  - respiratory symptoms: cough, sore throat, nasal congestion

Table 6: Characteristics of the studies included – RCT, direct comparison: baloxavir marboxil vs. oseltamivir, patients with an increased risk of a severe course of the disease (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

c. Influenza that did not require hospitalization at enrolment.
d. Presence of at least one of the following risk factors:

- asthma or chronic lung disease
- endocrine disorder (including diabetes mellitus)
- residents of long-term care facilities
- compromised immune system (including patients taking corticosteroids [≤ 20 mg prednisolone or equivalent] and patients under treatment for HIV infection, with CD4 count > 350 cells/mm^3 within the last 6 months)
- neurological and neurodevelopmental disorders
- cardiac disorders
- age ≥ 65 years
- American Indians and Alaskan Natives
- blood disorders
- metabolic disorders
- morbid obesity (BMI ≥ 40 kg/m^2)
- women who are within 2 weeks postpartum and are not breastfeeding

e. Onset of symptoms, defined as:

- time of the first increase in body temperature of at least 1° C from normal value
- time when at least one new general or respiratory symptom occurred

f. The arm is not relevant for the assessment and is no longer presented in the following tables.
g. Includes all patients who received the study drug, whose influenza diagnosis was confirmed by RT-PCR and who were enrolled at sites with GCP compliance.

AE: adverse event; BMI: body mass index; CD4: cluster of differentiation 4; GCP: good clinical practice; HIV: human immunodeficiency virus; ITTI: intention to treat infected; n: relevant subpopulation; N: number of randomized (included) patients; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction

Table 7: Characteristics of the intervention – RCT, direct comparison: baloxavir marboxil vs. oseltamivir, research question 2: patients with an increased risk of a severe course of the disease

Study	Intervention	Comparison
CAPSTONE-2	Baloxavir marboxil on day 1 ▪ 40 mg orally for < 80 kg body weight ▪ 80 mg orally for ≥ 80 kg body weight	Oseltamivir 75 mg orally in the morning and evening on days 1–5
	Non-permitted pretreatment ▪ peramivir, laninamivir, oseltamivir, zanamivir, rimantadine, umifenovir or amantadine within 30 days prior to the predose examination ▪ investigational product within 30 days (within 1 year in the case of monoclonal antibodies against a viral disease) prior to the predose examination ▪ systemic antimicrobial therapy for another infection at the time of the predose examination ▪ > 20 mg prednisolone or an equivalent dose of a systemic corticosteroid **Non-permitted concomitant treatment** ▪ systemic antiviral therapy[a] ▪ antimicrobial drugs (except for the treatment of complications of influenza during the course of the study that are presumably due to bacterial infection) and antimycotic drugs[b] ▪ antipyretics and analgesics[c] except paracetamol ▪ antitussives and expectorants ▪ combination cold preparations ▪ antihistamines[b] ▪ herbal drugs against influenza ▪ **Permitted concomitant treatment ("rescue therapy")** ▪ paracetamol of up to 3000 mg/day if influenza symptoms, such as fever, headache or muscle pain, are so severe that the patient needs symptomatic treatment[d]	

a. With the exception of antiretroviral drugs for the treatment of HIV infection or for suppression therapy of herpes simplex virus.
b. With the exception of topical application; application to the eyes, nose or ears and inhaled therapies were prohibited.
c. Low-dose acetylsalicylic acid was allowed as prophylaxis for cardiac disorders.
d. Paracetamol was provided by the sponsor. Its use had to be recorded by the patient in the electronic patient diary.

HIV: human immunodeficiency virus; RCT: randomized controlled trial

The CAPSTONE-2 study is a double-blind RCT on the comparison of baloxavir marboxil, oseltamivir and placebo. The study included patients aged ≥ 12 years with influenza confirmed by symptomatic diagnosis. Patients had to have at least one of the following risk factors for influenza-related complications: asthma or chronic lung disease, endocrine disorder (including diabetes mellitus), resident of long-term care facilities, compromised immune system, neurological and neurodevelopmental disorders, cardiac disorders, age ≥ 65 years, American Indians and Alaskan Natives, blood disorders, metabolic disorders, morbid obesity, and women who are within 2 weeks postpartum and are not breastfeeding. Patients with a severe course of the disease at enrolment were excluded. The patient population of the CAPSTONE-2 study thus represents the population of patients with uncomplicated influenza and an increased risk of a

severe course of the disease, which is the population relevant for research question 2. However, not all risk factors are covered. For example, patients with kidney and/or liver disease are missing from the definition of the risk population [14,15].

A total of 2184 patients were assigned in a 1:1:1 ratio to the 3 study arms of baloxavir marboxil, oseltamivir and placebo. The placebo arm is not relevant for the assessment in research question 2 of the benefit assessment and is not considered further. Randomization was stratified by symptom total score (≤ 14, ≥ 15), pre-existing and worsened symptom (yes, no), region (Asia, North America/Europe, Southern Hemisphere) and body weight (< 80 kg, ≥ 80 kg).

Baloxavir marboxil was administered in compliance with the SPC [8]. Oseltamivir was basically administered in compliance with the SPC [16]. According to the SPC, however, immunocompromised patients should be treated for a period of 10 days. In the CAPSTONE-2 study, however, they received uniform treatment over 5 days like all other patients. Since only 4% of the patients in the CAPSTONE-2 study had a compromised immune system, the deviation in dosing from the SPC in these patients is negligible for the interpretation of the results in the study.

Analogous to the studies JapicCTI-153090 and CAPSTONE-1, the use of antipyretics and analgesics was not allowed in the CAPSTONE-2 study, with the exception of paracetamol as "rescue therapy" if influenza symptoms, such as fever, headache or muscle pain, were so severe that the patient needed this therapy. Even when antiviral therapy is used, it is assumed that symptomatic therapy is also given. This is also in line with the company's note on the ACT, according to which it is assumed that supportive measures (e.g. sufficient hydration) as well as concomitant symptomatic therapy (e.g. antipyretics, antiphlogistics, analgesics) were carried out in both study arms. There is discrepant information in Module 4 A of the dossier on the proportion of patients taking paracetamol (around 3% and 8%). Overall, however, fewer than 10% of patients took paracetamol at least once. Due to the restricted use according to the study protocol, there was therefore severe overall limitation of concomitant symptomatic treatment in the CAPSTONE-2 study. This is taken into account in the assessment of the certainty of conclusions of the present study (see Section 2.4.2.2).

The primary outcome of the study was the time to alleviation of influenza symptoms (taking into account the change in pre-existing symptoms, see Section 2.4.2.1). Further patient-relevant outcomes were outcomes on symptoms, health status and AEs.

The study duration was 22 days. The patients conducted a daily recording of their symptoms in electronic patient diaries until day 14.

Analysis populations of the CAPSTONE-2 study

The company used different analysis populations for outcomes on morbidity and outcomes on side effects and mortality (deaths were recorded as part of the AE recording). The respective number of patients included can be found in Table 8.

Table 8: Analysis populations of the CAPSTONE-2 study – RCT, direct comparison: baloxavir marboxil vs. oseltamivir: patients with an increased risk of a severe course of the disease

Study Characteristic Category	Baloxavir marboxil	Oseltamivir
CAPSTONE-2		
Randomized patients, N	730	725
with influenza diagnosis confirmed by RT-PCR, n (%)	402 (55.1)	402 (55.4)
and who were enrolled at sites with GCP-compliant study conduct ("intention to treat infected [ITTI] population", according to the company)[a], n (%)	388 (53.2)	389 (53.7)
Safety population (at least one dose of study medication)[b], N	730[c]	721

a. Used by the company for analyses of morbidity outcomes.
b. Used by the company for analyses of harm outcomes (incl. mortality).
c. Including 3 patients randomized to another study arm (placebo or oseltamivir).
GCP: good clinical practice; n: number of patients in the subpopulation; N: number of patients in the respective population; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction

For the assessment of the morbidity outcomes, the company restricted the total population to patients who received the study drug, who had a documented influenza test by RT-PCR and who were enrolled at sites with good clinical practice (GCP) compliance. ("ITTI population"). Only few patients of the ITTI population (approx. 3%) were excluded because GCP standards were not implemented in 3 study centres. For the outcomes on side effects and mortality, the company analysed the patients who had received at least one dose of the study medication (safety population).

The approach of the company to use the ITTI population for the assessment of the outcome of the category of morbidity is not adequate. In clinical trials on the treatment of influenza, a distinction is usually made for morbidity outcomes between the analysis of all included patients regardless of a confirmed influenza diagnosis (ITT analysis) and the ITTI analysis, i.e. the analysis of the data of only those patients with subsequent confirmation by laboratory diagnostics of the influenza virus infection (after the start of treatment). For example, in one of the approval studies of oseltamivir in adults, the results of the relevant symptom outcomes were presented for both the ITT population and the ITTI population [17]. The analysis of the ITTI population would be relevant for the exclusive assessment of efficacy in the context of the approval; for the early benefit assessment, however, it is of interest how patients are treated in everyday health care. The analysis of the total population (ITT) without confirmed influenza diagnosis generally reflects the conditions in health care [15] because the diagnosis and subsequent treatment decision for antiviral treatment in clinical practice is generally not dependent on the laboratory diagnostic evidence of influenza [14,15,18]. Also, according to the SPC, no laboratory diagnostic evidence is required for the treatment of influenza with baloxavir marboxil and oseltamivir [8,16]. Accordingly, in the CAPSTONE-2 study, patients were

included in the study and treated regardless of laboratory diagnostic evidence. The present benefit assessment therefore uses the total population of the CAPSTONE-2 study for the benefit assessment of all outcome categories, i.e. including the outcomes on morbidity.

For this relevant analysis population, a change in the direction of zero effect can be assumed compared with effects for morbidity outcomes observed in the ITTI population. This is because in the absence of viral infection (e.g. confirmed by a negative RT-PCR test), the antiviral therapy cannot be assumed to be effective. A change in the effect from the ITTI to the ITT population in the direction of the zero effect was also shown in one of the approval studies on oseltamivir, for example for the outcome “disease duration” [17]. In the CAPSTONE-2 study, the ITTI population showed no statistically significant differences between the treatment groups in in the morbidity outcomes considered (see Appendix B of the full dossier assessment). Therefore, it is not to be expected overall that the consideration of the relevant analysis population would produce a different result in terms of statistical significance. In the present benefit assessment, the analyses of the ITTI population with influenza confirmed by RT-PCR are therefore taken into account in the description of the results and the conclusions on the added benefit on the basis of the relevant analysis population (ITT). The results of the ITTI population are presented as supplementary information in Appendix B of the full dossier assessment.

Patient characteristics

Table 9 shows the characteristics of the patients in the study included.

Table 9: Characteristics of the study populations – RCT, direct comparison: baloxavir marboxil vs. oseltamivir: patients with an increased risk of a severe course of the disease (multipage table)

Study Characteristic Category	Baloxavir marboxil	Oseltamivir
CAPSTONE-2	N[a] = 730	N[a] = 721
Age [years], mean (SD)	ND	ND
Age category [years], n (%)		
< 18	21 (3)	21 (3)
18–64	500 (68)	511 (71)
65–74	155 (21)	136 (19)
≥ 75	54 (7)	53 (7)
Sex [F/M], %	55/45	58/42
Geographical region, n (%)		
Asia	168 (23)	168 (23)
North America/Europe/Southern Hemisphere	562 (77)	553 (77)
Smoker, n (%)	ND	ND
Total symptom score[b], mean (SD)	ND	ND
Total symptom score[b], n (%)		
≤ 14	331 (45)	332 (46)
≥ 15	399 (55)	389 (54)
Time to treatment from onset of influenza [hours], n (%)	ND	ND
Influenza virus subtype by RT-PCR, n (%)[c]		
A/H1N1pdm	28 (4)	35 (5)
A/H3	182 (25)	190 (26)
B	167 (23)	149 (21)
Mixed infection	4 (< 1)	5 (< 1)
Other	7 (< 1)	10 (1)
No data	14 (2)[d]	13 (2)[d]
Negative	328 (45)[d]	323 (45)[d]
Risk factors for influenza-related complications[e], n (%)[c]	ND	ND
Respiratory/chronic lung disease	308 (42)	300 (41)
Endocrine disorder	232 (32)	243 (34)
Age ≥ 65 years	209 (29)	190 (26)
Cardiac disorder	83 (11)	78 (11)
Morbid obesity (BMI ≥ 40 kg/m^2)	75 (10)	96 (13)
Metabolic disorder	64 (9)	71 (10)
Neurological and neurodevelopmental disorders	45 (6)	50 (7)
Compromised immune system	26 (4)	26 (4)
Blood disorders	19 (3)	13 (2)
American Indians and Alaskan Natives	7 (< 1)	6 (< 1)
Resident of a long-term care facility	2 (< 1)	0 (0)

Table 9: Characteristics of the study populations – RCT, direct comparison: baloxavir marboxil vs. oseltamivir: patients with an increased risk of a severe course of the disease (multipage table)

Study Characteristic Category	Baloxavir marboxil	Oseltamivir
Within 2 weeks postpartum	1 (< 1)	0 (0)
Treatment discontinuation[f], n (%)	33 (5)	42 (6)
Study discontinuation, n (%)	ND	ND

a. Number of patients in the safety population (at least one dose of the study medication). Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. The symptom score (0-21 points) is composed of the 7 following symptoms: cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue, rated on a 4-point scale (0, none; 1, mild; 2, moderate; 3, severe).
c. Related to the randomized patients (N = 730 in the baloxavir marboxil arm and N = 725 in the oseltamivir arm).
d. Institute's calculation.
e. Several factors may be present at the same time.
f. Deviating from Module 4 A of the dossier, referred to as study discontinuations in Ison 2020 [12].

BMI: body mass index; F: female; ITTI: intention to treat infected; M: male; n: number of patients in the category; N: number of analysed patients; ND: no data; pdm: pandemic; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SD: standard deviation

Approximately 70% of the patients were between 18 and 65 years of age, 3% were younger than 18 years and 7% were ≥ 75 years. Around 80% of patients were treated in the region of North America/Europe/Southern Hemisphere. The most common risk factors for influenza-related complications were respiratory/chronic lung disease followed by endocrine disease (including diabetes mellitus) and age ≥ 65 years. 45% of all patients had a negative influenza test performed by RT-PCR. The 2 most common types of influenza were type A/H3 and type B.

The characteristics of the patients of the ITTI population are presented as supplementary information in Appendix B of the full dossier assessment.

Risk of bias across outcomes (study level)

Table 10 shows the risk of bias across outcomes (risk of bias at study level).

Table 10: Risk of bias across outcomes (study level) – RCT, direct comparison: baloxavir marboxil vs. oseltamivir

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			
CAPSTONE-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial							

The risk of bias across outcomes was rated as low for the CAPSTONE-2 study. This concurs with the company's assessment.

Transferability of the study results to the German health care context

The company conducted a joint assessment of the transferability of the study results to the German health care context with regard to general patient characteristics as well as disease-specific criteria for the 3 studies JapicCTI-153090, CAPSTONE-1 and CAPSTONE-2. It stated that the populations in the studies comprised a broad age range and both male and female patients. According to the company, characteristics such as weight and smoking status were comparable to those in Germany, the vaccination rate was slightly higher. In addition, the studies CAPSTONE-1 and CAPSTONE-2 included up to 50% Caucasians, with no indications that the course of influenza was clinically different depending on family origin. With regard to disease-specific criteria, the company compared the distribution of virus types in the CAPSTONE-2 study with the distribution of the corresponding season in Germany and concluded that transferability was given with regard to the virus (sub)types prevalent in the respective seasons of the studies. Overall, the company considered the study results to be 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.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

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

- Mortality
  - all-cause mortality

- Morbidity
  - influenza symptoms
  - health status measured with the European Quality of Life-5 Dimensions (EQ-5D) visual analogue scale (VAS)
  - influenza-typical complications
- Health-related quality of life
- Side effects
  - serious adverse events (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 A).

Table 11 shows for which outcomes data were available in the study included.

Table 11: Matrix of outcomes – RCT, direct comparison: baloxavir marboxil vs. oseltamivir

Study	Outcomes						
	All-cause mortality	Influenza symptoms[a]	Health status (EQ-5D VAS)	Influenza-typical complications[b]	Health-related quality of life	SAEs	Discontinuation due to AEs
CAPSTONE-2	Yes	No[c]	No[c]	No[c]	No[d]	Yes	Yes

a. Patient-reported symptoms include cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue.
b. Including death, hospitalization, sinusitis, bronchitis, otitis media and radiologically confirmed pneumonia.
c. No analyses for the total population relevant to the assessment (see Section 2.4.1.2); the results of the ITTI population presented in Appendix B of the full dossier assessment are additionally considered.
d. Outcome not recorded.

AE: adverse event; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; RCT: randomized controlled trial; SAE: serious adverse event

The total population of the CAPSTONE-2 study is relevant for the present benefit assessment. Results on morbidity outcomes including the outcome “influenza symptoms” described below

are only available for the ITTI population and are presented as supplementary information in Appendix B of the full dossier assessment.

Morbidity

Influenza symptoms

Influenza symptoms were recorded in an electronic patient diary once daily on days 1 as well as 10 to 14, and twice daily on days 2 to 9. For this purpose, the patients were asked to rate the following symptoms on a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe): cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, fatigue. Body temperature was measured 4 times daily until day 3 and 2 times daily until day 14.

The company presented analyses of the following operationalizations:

- Improvement of all influenza symptoms: taking into account potentially pre-existing symptoms (with consideration of the 3 symptoms of cough, fatigue and muscle or joint pain), improvement was defined as follows:
  - Pre-existing symptoms that had worsened with the onset of influenza and before administration of the study medication had to improve by at least one category during the course of the study.
  - Pre-existing symptoms that had not worsened with the onset of influenza and before administration of the study medication had to be maintained during the course of the study.
  - Symptoms that appeared for the first time at the onset of influenza had to improve by at least one category.

According to the statistical analysis plan, any change within the categories of "mild" and "no" symptoms was considered an improvement or, in the case of pre-existing symptoms, symptoms that had not worsened were considered maintained.

- Improvement in individual influenza symptoms; patients whose symptoms were rated 0 (none), 1 (mild), 2 (moderate) or 3 (severe) but already present and not worsened at baseline were excluded from the analysis.

The company presented analyses of the time to improvement in each case. Time to improvement of all (or of the individual) influenza symptoms was defined as the time at which the patient rated all (or the individual) influenza symptoms in accordance with the operationalization described above as improved or maintained for a duration of at least 21.5 hours (24 hours –10%). The study protocol predefined the time to improvement of all influenza symptoms as well as of the individual symptoms.

For the improvement of all influenza symptoms, the company also presented additional analyses of the proportion of patients with improvement for different time points.

Only the improvement of all symptoms is relevant for the present benefit assessment because the improvement of an individual symptom is not equivalent to a general improvement of the disease state. For example, the improvement of one symptom may be accompanied by the worsening of another symptom. Therefore, the analyses of individual symptoms (including the analysis of time to resolution of fever submitted by the company) are not considered. The analysis of the time to improvement of all symptoms based on the ITT population is relevant for the benefit assessment.

Furthermore, the time to recovery is, in principle, relevant for the present therapeutic indication (treatment of uncomplicated influenza). The company did not present such an analysis for the CAPSTONE-2 study in Module 4 A of the dossier.

2.4.2.2 Risk of bias

Table 12 describes the risk of bias for the results of the relevant outcomes.

Table 12: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: baloxavir marboxil vs. oseltamivir

Study	Study level	Outcomes						
		All-cause mortality	Influenza symptoms[a]	Health status (EQ-5D VAS)	Influenza-typical complications[b]	Health-related quality of life	SAEs	Discontinuation due to AEs
CAPSTONE-2	Low	Low	-[c]	-[c]	-[c]	-[d]	Low	Low

a. Patient-reported symptoms include cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue.
b. Including death, hospitalization, sinusitis, bronchitis, otitis media and radiologically confirmed pneumonia.
c. No analyses for the total population relevant to the assessment (see Section 2.4.1.2); the risk of bias of the results of the ITTI population presented as supplementary information in Appendix B of the full dossier assessment is rated as low.
d. Outcome not recorded.

AE: adverse event; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; RCT: randomized controlled trial; SAE: serious adverse event

The risk of bias of the results for the outcomes “all-cause mortality”, “SAEs” and “discontinuation due to AEs” was rated as low in each case. The assessment concurs with that of the company. For outcomes in the category of morbidity, no analyses are available for the total population relevant to the assessment. For the results of the ITTI population considered as supplementary information in Appendix B of the full dossier assessment, the risk of bias for the

results of the morbidity outcomes was rated as low. However, due to the restriction of concomitant symptomatic treatment in the CAPSTONE-2 study (see Section 2.4.1.2), no more than hints can be derived for all outcomes.

2.4.2.3 Results

Table 13 to Table 15 summarize the results of the comparison of baloxavir marboxil against oseltamivir in patients with an increased risk of a severe course of the disease. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier.

The results of the total population of the CAPSTONE-2 study relevant for the benefit assessment are presented (for justification, see Section 2.4.1.2). Results of the ITTI population are presented as supplementary information in Appendix B of the full dossier assessment.

Tables with common AEs, SAEs and discontinuations due to AEs can be found in Appendix C of the full dossier assessment.

Table 13: Results (mortality, morbidity, side effects, dichotomous) – RCT, direct comparison: baloxavir marboxil vs. oseltamivir

Study Outcome category Outcome	Baloxavir marboxil		Oseltamivir		Baloxavir marboxil vs. oseltamivir
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value[a]
CAPSTONE-2					
Mortality					
All-cause mortality	730	0 (0)	721	1 (0.1)	0.33 [0.01; 8.07][b]; 0.370
Morbidity					
Influenza-typical complications[c]	No results for the relevant analysis population[d]				
Health-related quality of life	Outcome not recorded				
Side effects					
AEs (supplementary information)	730	179 (24.5)	721	192 (26.6)	–
SAEs	730	5 (0.7)	721	8 (1.1)	0.62 [0.20; 1.88]; 0.530
Discontinuation due to AEs	730	5 (0.7)	721	4 (0.6)	1.23 [0.33; 4.58]; 0.828

a. Institute's calculation, unconditional exact test (CSZ method according to [19]).
b. Institute's calculation of RR and CI (asymptotic); since no events occurred in the baloxavir marboxil arm, the calculation used the correction term of 0.5 in both study arms.
c. Including death, hospitalization, sinusitis, bronchitis, otitis media and radiologically confirmed pneumonia.
d. The company only presented results for the ITTI population with positive influenza detection by RT-PCR. The results are presented as supplementary information in Appendix B of the full dossier assessment. No statistically significant differences between treatment groups were shown in the ITTI population. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment.

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

Table 14: Results (morbidity, time to event) – RCT, direct comparison: baloxavir marboxil vs. oseltamivir

Study Outcome category Outcome	Baloxavir marboxil		Oseltamivir		Baloxavir marboxil vs. oseltamivir
	N	Median time to event in hours [95% CI] Patients with event n (%)	N	Median time to event in hours [95% CI] Patients with event n (%)	HR [95% CI]; p-value
CAPSTONE-2					
Morbidity					
Influenza symptoms[a]	No results for the relevant analysis population[b]				

a. Time to improvement of all influenza symptoms. Patient-reported symptoms include cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue.
b. The company only presented results of the ITTI population with positive influenza detection by RT-PCR. The results are presented as supplementary information in Appendix B of the full dossier assessment. No statistically significant differences between treatment groups were shown in the ITTI population. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment.

CI: confidence interval; HR: hazard ratio; ITTI: intention to treat infected; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction

Table 15: Results (morbidity, continuous) – RCT, direct comparison: baloxavir marboxil vs. oseltamivir

Study Outcome category Outcome	Baloxavir marboxil			Oseltamivir			Baloxavir marboxil vs. oseltamivir
	N	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean (SE)	MD [95% CI]; p-value
CAPSTONE-2							
Morbidity							
Health status (EQ-5D VAS)	No results for the relevant analysis population[a]						

a. The company only presented results of the ITTI population with positive influenza detection by RT-PCR. The results are presented as supplementary information in Appendix B of the full dossier assessment. No statistically significant differences between treatment groups were shown in the ITTI population. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment.

CI: confidence interval; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; ITTI: intention to treat infected; MD: mean difference; N: number of analysed patients; RCT: randomised controlled trial; RT-PCR: reverse transcriptase polymerase chain reaction; SD: standard deviation

On the basis of the available data, no more than hints, e.g. of an added benefit, can be determined for all outcomes.

Mortality

All-cause mortality

There was no statistically significant difference between the treatment arms for the outcome "all-cause mortality". This resulted in no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for this outcome; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Influenza symptoms

Operationalization

Event time analyses of the improvement of all symptoms are relevant for the present benefit assessment.

Result

For the relevant analysis population, no results are available for the assessment of the added benefit of the influenza symptoms. No statistically significant difference between treatment groups was shown in the ITTI population presented as supplementary information in Appendix B of the full dossier assessment. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment (see Section 2.4.1.2). Therefore, it is not to be expected that the consideration of the relevant analysis population would produce a different result in terms of statistical significance. Overall, this resulted in no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for the outcome "influenza symptoms"; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also derived no added benefit. The company based its assessment on the results of the ITTI population, however, and also used further operationalizations.

Health status (EQ-5D VAS)

Operationalization

The analyses of the mean change from baseline are relevant for the present benefit assessment.

The responder analyses presented by the company on the proportion of patients with an improvement of ≥ 7 or 10 points are not a meaningful operationalization in the present situation. Responder analyses at a point in time at the end of the study are not meaningful in the case of a short acute illness, as it can be expected that the majority of patients with an increased risk of a severe course of the disease (according to research question 2 of the present benefit

assessment) will recover completely. Furthermore, it is not meaningfully possible to select a specific point in time. Event time analyses using a response criterion corresponding to 15% of the scale range are not available.

The company only presented results for the ITTI population.

Result

No results are available for the relevant analysis population. No statistically significant difference between treatment groups was shown in the ITTI population presented as supplementary information in Appendix B of the full dossier assessment. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment (see Section 2.4.1.2). Overall, this resulted in no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for the outcome "health status"; an added benefit is therefore not proven.

This is concurs with the assessment of the company in that the company also did not derive an added benefit based on the responder analysis of an improvement of ≥ 10 points in the ITTI population.

Influenza-typical complications

Operationalization

Influenza-typical complications were recorded in the CAPSTONE-2 study based on the proportion of patients who experienced the following AEs after the start of the study: death, hospitalization, sinusitis, bronchitis, otitis media and radiologically confirmed pneumonia. The present benefit assessment uses the entirety of influenza-typical complications; the individual complications are not considered separately.

Result

No results are available for the relevant analysis population. No statistically significant difference between treatment groups was shown in the ITTI population presented as supplementary information in Appendix B of the full dossier assessment. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment (see Section 2.4.1.2). Overall, this resulted in no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for influenza-typical complications; an added benefit is therefore not proven.

This concurs with the assessment of the company insofar as the company also derived no added benefit based on the ITTI population.

Health-related quality of life

The outcome "health-related quality of life" was not recorded in the CAPSTONE-2 study.

Side effects

SAEs and discontinuation due to AEs

There was no statistically significant difference between the treatment arms 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 oseltamivir for either of these outcomes; greater or lesser harm is therefore not proven.

This concurs with the company's assessment.

2.4.2.4 Subgroups and other effect modifiers

The following subgroup characteristics were considered for the present assessment:

- sex (female versus male)
- age (< 18 years versus 18 years to ≤ 64 years versus 65 years to ≤ 74 years versus ≥ 75 years)
- time to treatment from influenza onset (0 to ≤ 12 hours versus > 12 to ≤ 24 hours versus < 24 to ≤ 36 hours versus < 36 to ≤ 48 hours)

All subgroup characteristics considered were prespecified in the CAPSTONE-2 study.

In the present benefit assessment, subgroup analyses are only considered for the total population. For these, the company only presented corresponding analyses for outcome in the category of side effects. Furthermore, of the subgroup characteristics used for the benefit assessment, analyses are only available for age and sex.

The company presented no subgroup analyses for the outcome "all-cause mortality". This is appropriate as only one event occurred in the total population.

Interaction tests were performed when at least 10 patients per subgroup were included in the analysis. Moreover, for binary data, there must 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. Where necessary, an interaction test (Q test) was carried out in the Institute's calculation.

There were no statistically significant interactions between treatment and subgroup characteristic for the outcomes "SAEs" and "discontinuation due to AEs".

2.4.3 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.

2.4.3.1 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 2.4.2 (see Table 16).

Table 16: Extent of added benefit at outcome level: baloxavir marboxil vs. oseltamivir

Outcome category **Outcome**	**Baloxavir marboxil vs. oseltamivir** **Proportion of events (%) or time to event (median in hours) or mean change over the course of the study (mean)** **Effect estimation [95% CI];** **p-value** **Probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0.1% RR: 0.33 [0.01; 8.07] p = 0.370	Lesser benefit/added benefit not proven
Morbidity		
Influenza symptoms[c]	No results for the relevant analysis population[d]	Lesser benefit/added benefit not proven
Influenza-typical complications[e]	No results for the relevant analysis population[d]	Lesser benefit/added benefit not proven
Health status		
EQ-5D VAS	No results for the relevant analysis population[d]	Lesser benefit/added benefit not proven
Health-related quality of life		
Outcome not recorded		
Side effects		
SAEs	0.7% vs. 1.1% RR: 0.62 [0.20; 1.88] p = 0.530	Greater/lesser harm not proven
Discontinuation due to AEs	0.7% vs. 0.6% RR: 1.23 [0.33; 4.58] p = 0.828	Greater/lesser harm not proven

a. Probability provided if statistically significant differences are present.
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. The reported symptoms include cough, sore throat, headache, nasal congestion, fever or chills, muscle or joint pain, and fatigue.
d. The company only presented results of the ITTI population with positive influenza detection by RT-PCR. The results are presented as supplementary information in Appendix B of the full dossier assessment. No statistically significant differences between treatment groups were shown in the ITTI population. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment.
e. Including death, hospitalization, sinusitis, bronchitis, otitis media and radiologically confirmed pneumonia.

AE: adverse event; CI: confidence interval; CI_u: upper limit of the confidence interval; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; HR: hazard ratio; ITTI: intention to treat infected; MD: mean difference; RR: relative risk; RT-PCR: reverse transcriptase polymerase chain reaction; SAE: serious adverse event

2.4.3.2 Overall conclusion on added benefit

Table 17 summarizes the results considered in the overall conclusion on the extent of added benefit.

Table 17: Positive and negative effects from the assessment of baloxavir marboxil in comparison with oseltamivir: patients with an increased risk of a severe course of the disease

Positive effects	Negative effects
–	–
The company did not present any results on the total population for the outcome category of morbidity. In the ITTI population with a positive influenza test using RT-PCR, there were no statistically significant differences between the treatment groups. Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population relevant for the assessment. Outcomes from the category of health-related quality of life were not recorded. ITTI: intention to treat infected; RT-PCR: reverse transcriptase polymerase chain reaction	

The CAPSTONE-2 study showed no positive or negative effects for patients with an increased risk of a severe course of the disease in the population with influenza confirmed by symptomatic diagnosis relevant for the benefit assessment, irrespective of laboratory diagnostic evidence. No results are available for the relevant population for morbidity outcomes (influenza symptoms, health status and influenza-typical complications). There were no statistically significant differences between the treatment groups for any of these 3 outcomes in the population of patients who tested positive for influenza (confirmed by RT-PCR). Compared with the effect in the ITTI population, a change of the effect in the direction of zero effect can be assumed for the total population. Therefore, it is not to be expected that the consideration of the relevant analysis population would produce a different result in terms of statistical significance.

In summary, there is no hint of an added benefit of baloxavir marboxil in comparison with oseltamivir for patients aged 12 years and above with uncomplicated influenza if there is an increased risk of a severe course of the disease.

The assessment deviates from that of the company, which derived an indication of a minor added benefit. The company based the added benefit of baloxavir marboxil in comparison with oseltamivir on laboratory diagnostic parameters (time to cessation of viral shedding, proportion of patients positive for influenza virus titer after 24, 48 and 72 hours).

2.5 Probability and extent of added benefit – summary

Table 18 summarizes the result of the assessment of the added benefit of baloxavir marboxil in comparison with the ACT.

Table 18: Baloxavir marboxil – probability and extent of added benefit

Subindication	**ACT**[a]	**Probability and extent of added benefit**
Patients aged 12 years and above with uncomplicated influenza without risk of influenza-related complications	Symptomatic therapy (antipyretics, antiphlogistics, analgesics)[b]	Added benefit not proven
Patients aged 12 years and above with uncomplicated influenza if there is an increased risk of a severe course of the disease	Antiviral therapy **(oseltamivir** or zanamivir)[b, c]	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. In cases where the company, because of the G-BA's specification of the ACT, could choose a comparator therapy from several options, the respective choice of the company is printed in **bold**. b. It is assumed that supportive measures (e.g. sufficient hydration) as well as concomitant symptomatic therapy (e.g. antipyretics, antiphlogistics, analgesics) are carried out in both study arms. c. 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 treatment of influenza. ACT: appropriate comparator therapy; 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.

1. Institute for Quality and Efficiency in Health Care. General methods 6.0 (German version) [online]. 2020 [Accessed: 27.01.2021]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-6-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. Shionogi. A randomized, double-blind, placebo-controlled, phase 2 study of S-033188 in otherwise healthy adult patients with influenza [online]. 2016 [Accessed: 01.03.2021]. URL: https://www.clinicaltrials.jp/user/showCteDetailE.jsp?japicId=JapicCTI-153090.

4. 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. https://dx.doi.org/10.1056/NEJMoa1716197.

5. Watanabe A, Ishida T, Hirotsu N et al. Baloxavir marboxil in Japanese patients with seasonal influenza: Dose response and virus type/subtype outcomes from a randomized phase 2 study. Antiviral Res 2019; 163: 75-81. https://dx.doi.org/10.1016/j.antiviral.2019.01.012.

6. Shionogi. A Study of S-033188 (Baloxavir Marboxil) Compared With Placebo or Oseltamivir in Otherwise Healthy Patients With Influenza [online]. 2019 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT02954354.

7. Uehara T, Hayden FG, Kawaguchi K et al. Treatment-Emergent Influenza Variant Viruses With Reduced Baloxavir Susceptibility: Impact on Clinical and Virologic Outcomes in Uncomplicated Influenza. J Infect Dis 2020; 221(3): 346-355. https://dx.doi.org/10.1093/infdis/jiz244.

8. Roche. Xofluza [online]. 2021 [Accessed: 06.04.2021]. URL: https://www.fachinfo.de.

9. Ratiopharm. Paracetamol-ratiopharm 500 mg Tabletten [online]. 2018 [Accessed: 30.04.2021]. URL: https://www.ratiopharm.de/assets/products/de/label/Paracetamol-ratiopharm%20500%20mg%20Tabletten%20-%202.pdf.

10. Shionogi. Study of S-033188 (Baloxavir Marboxil) Compared With Placebo or Oseltamivir in Patients With Influenza at High Risk of Influenza Complications (CAPSTONE 2) [online]. 2019 [Accessed: 01.03.2021]. URL: https://ClinicalTrials.gov/show/NCT02949011.

11. Shionogi. A Phase 3, Multicenter, Randomized, Double-blind Study of a Single Dose of S-033188 Compared with Placebo or Oseltamivir 75 mg Twice Daily for 5 Days in Patients with Influenza at High Risk of Influenza Complications [online]. [Accessed: 01.03.2021]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2016-002688-32.

12. Ison MG, Portsmouth S, Yoshida Y et al. Early treatment with baloxavir marboxil in high-risk adolescent and adult outpatients with uncomplicated influenza (CAPSTONE-2): a randomised, placebo-controlled, phase 3 trial. Lancet Infect Dis 2020; 20(10): 1204-1214. https://dx.doi.org/10.1016/S1473-3099(20)30004-9.

13. Center For Drug Evaluation and Research. XOFLUZA 20 mg and 40 mg tablets: Approval Package; Application Number: c210854Orig1s001 [online]. 2019 [Accessed: 01.04.2021]. URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/210854Orig1s001.pdf.

14. Centers for Disease Control and Prevention. Influenza Antiviral Medications: Summary for Clinicians [online]. 2021 [Accessed: 14.04.2021]. URL: https://www.cdc.gov/flu/professionals/antivirals/summary-clinicians.htm.

15. Robert Koch-Institut. Nationaler Pandemieplan Teil II; Wissenschaftliche Grundlagen [online]. 2016 [Accessed: 14.04.2021]. URL: https://www.rki.de/DE/Content/InfAZ/I/Influenza/Pandemieplanung/Downloads/Pandemieplan_Teil_II_gesamt.pdf?__blob=publicationFile.

16. Roche. Tamiflu 30 mg/45 mg/75 mg Hartkapseln [online]. 2020 [Accessed: 14.04.2021]. URL: https://www.fachinfo.de.

17. Nicholson KG, Aoki FY, Osterhaus AD et al. Efficacy and safety of oseltamivir in treatment of acute influenza: a randomised controlled trial. Neuraminidase Inhibitor Flu Treatment Investigator Group. Lancet 2000; 355(9218): 1845-1850. https://dx.doi.org/10.1016/s0140-6736(00)02288-1.

18. Robert Koch-Institut. Influenza (Teil 1): Erkrankungen durch saisonale Influenzaviren; RKI-Ratgeber [online]. 2018 [Accessed: 14.04.2021]. URL: https://www.rki.de/DE/Content/Infekt/EpidBull/Merkblaetter/Ratgeber_Influenza_saisonal.html.

19. Martín Andrés A, Silva Mato A. Choosing the optimal unconditioned test for comparing two independent proportions. Computat Stat Data Anal 1994; 17(5): 555-574. https://dx.doi.org/10.1016/0167-9473(94)90148-1.

The full report (German version) is published under https://www.iqwig.de/en/projects/a21-21.html.