IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

IQWiG Reports – Commission No. A14-29

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Propranolol – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 26 November 2014). 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.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Propranolol – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
29 August 2014

Internal Commission No.:
A14-29

Address of publisher:
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Keywords: propranolol, hemangioma, benefit assessment

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[3] 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
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
PT	MedDRA Preferred Term
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	MedDRA System Organ Class
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 propranolol. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 29 August 2014.

Research question

The aim of this report is to assess the added benefit of propranolol in comparison with the appropriate comparator therapy (ACT) in patients with proliferating infantile haemangioma requiring systemic therapy: life- or function-threatening haemangioma, ulcerated haemangioma with pain and/or lack of response to simple wound care measures, haemangioma with a risk of permanent scars or disfigurement.

The G-BA specified individual treatment as ACT. The specifications of the respective Summaries of Product Characteristics (SPCs) of the drugs used for treatment are to be taken into account. The company primarily concurred with the G-BA's specification, but further specified that it considered watchful waiting to be the only treatment option for individual treatment.

Watchful waiting in the sense of individual treatment may be a potential ACT for a subpopulation in the therapeutic indication of propranolol. In the present therapeutic indication, however, other individual treatment options are also conceivable (e.g. glucocorticoids for a subindication of the therapeutic indication of propranolol). The company's specifications excluded these potential treatment options.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The implementation of individual treatment in the studies was examined. The assessment was conducted based on patient-relevant outcomes and on direct comparative randomized controlled trials (RCTs).

Results

One relevant study (V00400SB 201) was available for the benefit assessment. This was a double-blind, placebo-controlled, multicentre phase 2/3 approval study of propranolol. Children aged 35 to 150 days with proliferating infantile haemangioma that requires systemic therapy and has not been previously treated were included in the study. Children with life- or function-threatening infantile haemangioma and children with ulcerated infantile haemangioma with pain and lack of response to simple wound care measures were excluded from participation in the study.

Since only patients with infantile haemangioma with a risk of permanent scars or disfigurement were investigated in the study, the V00400SB 201 study could only be used for assessing the added benefit in this subpopulation.

Watchful waiting might be discussed as individual treatment for this subpopulation of the therapeutic indication of propranolol. It was therefore examined whether the administration of placebo in the V00400SB 201 study can be assessed as watchful waiting and whether watchful waiting is an option for the patient population investigated in the sense of individual treatment.

According to the study protocol, any drug or non-drug interventions for the treatment of infantile haemangioma were prohibited in both arms of the study (both in the treatment phase and during follow-up). The evolution of the target and non-target haemangioma was assessed by a physician at regular intervals. If it was considered to be medically necessary, study treatment could be discontinued and necessary interventions could be initiated. These requirements were overall considered to be sufficient in the framework of watchful waiting because close monitoring was planned for the early detection of any complications and initiation of necessary interventions.

Moreover it was assumed that watchful waiting (with administration of placebo) is an adequate treatment option in the sense of individual treatment for the patient population investigated in the study. It can be assumed for the patients investigated in the study that, based on the patient's history and clinical assessment, immediate treatment was not strictly required at the time point of their enrolment in the study. In this context, the informed consent obtained from the parents or guardians was interpreted in such a way that they had agreed to the possibility of waiting under close monitoring. At the same time, the information provided in the study documents did not indicate that a broad range of therapeutic interventions was used after completion or discontinuation of the study treatment.

Risk of bias

The risk of bias at study level was rated as low for the V00400SB 201 study so that, in principle, indications of added benefit could be derived from it.

The risk of bias was rated as high for all patient-relevant outcomes for which evaluable results were presented in the dossier. The fact that notably more patients discontinued treatment and the study early in the placebo arm than in the propranolol arm was decisive for assessing the risk of bias as high. For the outcomes on the resolution of the target haemangioma, sensitivity analyses showed that no doubts were raised about the magnitude of the resulting effect so that, overall, the high risk of bias for these outcomes did not result in downgrading the certainty of conclusions.

Mortality

All-cause mortality

No deaths were observed in the study. Due to the risk of bias, the only conclusion to be derived for this outcome was that the available data showed no greater harm from propranolol. Hence an added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to the outcome "all-cause mortality" is not proven.

Morbidity

Complete/nearly complete resolution of the target haemangioma at week 24

Several analyses, which consistently showed a statistically non-significant result, were used for the outcome "complete/nearly complete resolution of the target haemangioma at week 24 (evaluation by the investigator based on clinical examinations and photographic documentation)". Overall, there was no added benefit of propranolol in comparison with watchful waiting (with administration of placebo).

Complete/nearly complete resolution of the visible component of the target haemangioma at week 24

Several analyses were used for the outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24 (centralized evaluation based on the photographs)". All analyses showed a statistically significant effect in favour of propranolol. Overall, there is an indication of an added benefit of propranolol in comparison with watchful waiting (with administration of placebo).

Time to first sustained complete/nearly complete resolution of the target haemangioma

Due to the notable differences in treatment durations between the study arms and the associated high informative bias, there were no evaluable data for the outcome "time to first sustained complete/nearly complete resolution of the target haemangioma".

Target haemangioma complications

Based on the naive proportions of patients with event, there was no statistically significant difference between the treatment arms for the outcome "target haemangioma complications" (functional impairment, ulceration and bleeding). It could only be concluded for this outcome that the data presented showed no greater or lesser benefit despite the bias to the disadvantage of propranolol. Hence the added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to target haemangioma complications is not proven.

Complete resolution of the non-target haemangioma

There were no evaluable data for the outcomes "complete resolution of the non-target haemangioma (facial)" and "complete resolution of the non-target haemangioma (non-facial)" because the number of events could not be clearly derived according to the intention to treat

(ITT) principle from the information provided in the clinical study report (CSR). Hence the added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to the complete resolution of the non-target haemangioma is not proven.

Health-related quality of life

Health-related quality of life was not investigated in the study. An added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to health-related quality of life is not proven.

Adverse events (AEs)

Serious adverse events (SAEs)

Based on the naive proportions of patients with event, there was no statistically significant difference between the treatment arms with regard to the outcome "SAEs". It could only be concluded for this outcome that the data presented showed no greater harm despite the bias to the disadvantage of propranolol. Hence greater or lesser harm from propranolol in comparison with watchful waiting (with administration of placebo) with regard to SAEs is not proven.

Discontinuation due to AEs

Based on the naive proportions of patients with event, there was a statistically significant difference between the treatment arms in favour of propranolol with regard to discontinuation due to AEs. However, the results also included events that could be attributed to the worsening of the haemangioma or lack of efficacy of the study medications. Overall, a conclusion could be derived that the available data showed no greater harm from propranolol regarding discontinuation due to AEs. Greater or lesser harm from propranolol in comparison with watchful waiting (with administration of placebo) is not proven for this outcome.

Bronchospasm

Based on the naive proportions of patients with event, there was no statistically significant difference between the treatment arms with regard to the outcome "bronchospasm". Hence greater or lesser harm from propranolol in comparison with watchful waiting (with administration of placebo) with regard to bronchospasm is not proven.

Infections and infestations and diarrhoea

Based on the naive proportions of patients with event, there was a statistically significant effect to the disadvantage of propranolol for the outcomes "infections and infestations" and "diarrhoea". Also under consideration of the direction of the bias to the disadvantage of propranolol, potential harm from propranolol cannot be completely excluded for these outcomes.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[4]

On the basis of the results presented, the extent and probability of the added benefit of the drug propranolol compared with the ACT is assessed as follows:

Based on the available results, a positive effect (indication) of propranolol remains for the outcome category "serious/severe symptoms" (outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24").

On the negative side, only a qualitative interpretation of the results could be conducted because of a notable difference in treatment duration between the study arms. There was a statistically significant effect to the disadvantage of propranolol for the outcomes "diarrhoea" and "infections and infestations". Despite the direction of the bias (to the disadvantage of propranolol), potential harm from propranolol could not be completely excluded.

The available results, however, did not provide signs of harm due to diarrhoea and infections and infestations in a magnitude that would justify downgrading the added benefit of propranolol. This is particularly justified by the size of the effect regarding benefit for the outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24". At the same time, most AEs were classified as non-serious. Moreover, the ratio of occurrence of diarrhoea and infections and infestations in the study arms roughly corresponded to the ratio of treatment duration in the 2 relevant study arms.

A conclusion on the added benefit of propranolol can be derived from the V00400SB 201 study for the subpopulation of patients with proliferating infantile haemangioma requiring systemic therapy with a risk of permanent scars or disfigurement for whom watchful waiting in the sense of individual treatment is an option as ACT. Overall, there is an indication of major added benefit of propranolol versus the ACT watchful waiting for the patients of this subpopulation.

For the other subpopulations of the therapeutic indication, an added benefit is not proven.

Table 2 presents a summary of the extent and probability of the added benefit of propranolol.

[4] 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), see [1]. 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, no added benefit, or less benefit), see [2].

Table 2: Propranolol – extent and probability of added benefit

Therapeutic indication	**ACT**[a]	**Extent and probability of added benefit**
Treatment of proliferating infantile haemangioma requiring systemic therapy:		
Life- or function-threatening haemangioma	Individual treatment. The specifications of the respective SPCs of the drugs used for treatment are to be taken into account.	Added benefit not proven
Ulcerated haemangioma with pain and/or lack of response to simple wound care measures		Added benefit not proven
Haemangioma with a risk of permanent scars or disfigurement		Indication of a major added benefit[b]

a: Presentation of the ACT specified by the G-BA.
b: For patients in whom watchful waiting in the sense of individual treatment is an option as ACT.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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

2.2 Research question

The aim of this report is to assess the added benefit of propranolol in comparison with the ACT in patients with proliferating infantile haemangioma requiring systemic therapy: life- or function-threatening haemangioma, ulcerated haemangioma with pain and/or lack of response to simple wound care measures, haemangioma with a risk of permanent scars or disfigurement [3].

The G-BA specified individual treatment as ACT. The specifications of the respective SPCs of the drugs used for treatment are to be taken into account.

The company primarily concurred with the G-BA's specification, but further specified that it considered watchful waiting to be the only treatment option for individual treatment.

This assessment by the company was not accepted. Watchful waiting in the sense of individual treatment may be a potential ACT for a subpopulation in the therapeutic indication of propranolol. This would be conceivable in patients, for example, for whom no concrete therapeutic interventions are available in the individual case, or in patients in whom immediate treatment is not strictly required because of the patient's history and clinical assessment. Within the approved use of propranolol, watchful waiting would not be suitable in life- or function-threatening or ulcerated haemangioma, but may be an option in haemangioma with risk of permanent scars or disfigurement. However, the company did not describe these patient groups and considered watchful waiting to be the only treatment option, irrespective of the individual case.

In the present therapeutic indication, other individual treatment options are also conceivable (e.g. glucocorticoids for a subindication of the therapeutic indication of propranolol). The company's specifications excluded these potential treatment options (see Section 2.7.1 of the full dossier assessment).

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The implementation of individual treatment in the studies was examined.

The assessment was conducted based on patient-relevant outcomes and on direct comparative RCTs.

2.3 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 lists on propranolol (studies completed up to 9 July 2014)
- bibliographical literature search on propranolol (last search on 30 July 2014)
- search in trial registries for studies on propranolol (last search on 9 July 2014)

To check the completeness of the study pool:

- search in trial registries for studies on propranolol (last search on 18 September 2014)

One additional study was identified from the check (EudraCT 2009-017241-55), in which propranolol was investigated in comparison with prednisone [4]. Based on the information provided in the trial registry, this study could not be excluded with certainty. The company excluded this RCT in its search because of the intervention and of the comparator therapy. This was not comprehensible, but had no consequence for the benefit assessment because there were no results in the trial registry that could be used for the benefit assessment.

2.3.1 Studies included

The study listed in the following table (V00400SB 201) was included in the benefit assessment.

Table 3: Study pool – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
V00400SB 201	Yes	Yes	No
a: Study for which the company was sponsor, or in which the company was otherwise financially involved. RCT: randomized controlled trial; vs.: versus			

The V00400SB 201 study was used by the company for the comparison with watchful waiting. Under certain conditions, watchful waiting may be discussed as individual treatment (see Section 2.3.2).

Children with life- or function-threatening and ulcerated haemangioma with pain and lack of response to simple wound care measures were excluded from this study, however. The company additionally presented the results of further investigations in the dossier to also consider studies with this patient population (with haemangioma of a higher severity grade). However, the further investigations presented by the company were unsuitable to assess an added benefit of propranolol in comparison with the ACT (see Section 2.7.2.7 of the full dossier assessment).

Section 2.6 contains a reference list for the study included.

2.3.2 Study characteristics

Table 4 and Table 5 describe the study used for the benefit assessment.

Table 4: Characteristics of the study included – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[f]
V00400SB 201	RCT, double-blind, placebo-controlled, multicentre, phase 2/3 study[a], randomized in a ratio of 2:2:2:2:1[b]	Children aged 35 to 150 days with proliferative IH requiring systemic therapy[c]	▪ Propranolol 1 mg/kg/day for 3 months[d] (N = 99) ▪ propranolol 1 mg/kg/day for 6 months (N = 103) ▪ propranolol 3 mg/kg/day for 3 months[d] (N = 101) ▪ propranolol 3 mg/kg/day for 6 months (N = 102) ▪ placebo for 6 months (N = 55) Relevant study arms thereof: ▪ propranolol 3 mg/kg/day for 6 months[e] (N = 102) ▪ placebo for 6 months (N = 55)	Treatment duration: 24 weeks (6 months) Observation period: up to week 96	56 centres in 16 countries (Australia, Canada, Czech Republic, France, Germany, Hungary, Italy, Lithuania, Mexico, New Zealand, Peru, Poland, Romania, Russian Federation, Spain, United States) Study period: 2/2010–11/2013	Primary outcome: complete/nearly complete resolution of the visible component of the target haemangioma at week 24[g] Secondary outcomes: complete/nearly complete resolution of the target haemangioma at week 24[h], time to first sustained complete/nearly complete resolution of the target haemangioma, complete resolution of the non-target haemangioma, target haemangioma complications, adverse events

a: The V00400SB 201 study was a phase 2/3 study with adaptive 2 stage design. At the end of stage 1 (corresponding to phase 2), the treatment regimen (dose and treatment duration) that was to be continued in stage 2 (corresponding to phase 3) was chosen based on the results of the interim analysis.
b: According to the information of amendment PA02 to the study protocol (8/2010), the randomization ratio was changed from 1:1:1:1:1 to 2:2:2:2:1 to reduce the number of patients allocated to the placebo arm. At this time point, 12 patients of the placebo arm (21.8%) and 13 patients of the relevant propranolol arm 3 mg/kg for 6 months (12.7%) were already included in the original randomization ratio.
c: According to the exclusion criteria of the study, patients with life-threatening of function-threatening IH and patients with ulcerated IH with pain and lack of response to simple wound care measures, among others, were excluded from the study.
d: After 3-month treatment with propranolol, patients received placebo for another 3 months.
e: Only the patients from the study arm with approval-compliant treatment with 3 mg/kg/day for 6 months were included in this assessment.
f: Primary outcomes contain information without consideration of its relevance for the present benefit assessment. Secondary outcomes exclusively contain information on the relevant available outcomes for this benefit assessment.
g: The primary outcome was assessed on the basis of the comparison of photographs at the start of the study and at week 24 in a centralized evaluation by 2 independent readers.
h: Evaluation by the investigator based on clinical examinations and photographic documentation.
IH: infantile haemangioma; N: number of randomized patients; RCT: randomized controlled trial; vs.: versus

Table 5: Characteristics of the interventions – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study	Intervention	Comparison	Concomitant medication and therapeutic interventions (in both study arms)
V00400SB 201	Propranolol oral solution in 2 separate doses (morning and late afternoon) for a total of 24 weeks (6 months): ▪ week 1: 1 mg/kg/day ▪ week 2: 2 mg/kg/day ▪ from week 3: 3 mg/kg/day	Placebo oral solution in 2 separate doses (morning and late afternoon) for a total of 24 weeks (6 months) sham titration	Permitted medication: all drugs that were not prohibited (see below) If drugs or interventions were necessary to treat the IH for medical reasons, they had to be documented in the eCRF. Treatment with the study medication had to be discontinued.
			Prohibited medication/therapeutic interventions[a]: corticosteroids[b] (systemic, intra-lesional or topical), imiquimod, vincristine[b], alfa interferon[b], propranolol or other beta-blockers[c], any interventions for the treatment of the IH (including any surgical and/or medical procedures such as laser therapy)
			Observation measures specified in the study: regular physical examination[d] and examination of the IH[d], evaluation of the target haemangioma for functional complications, ulceration and bleeding[d]

a: These medications and therapeutic interventions were prohibited both at any time before enrolment of the child into the study and during the total study duration (96 weeks).
b: These medications were also prohibited for the mothers 14 days before randomization and during the total study duration (96 weeks) if they were breastfeeding their children.
c: These medications were also prohibited for the mothers any time before enrolment and during the total study duration (96 weeks) if they were breastfeeding their children.
d: Treatment phase: weekly examination in the first 3 weeks, then in week 5 and 8, and every 4 weeks up to week 24. Follow-up: in weeks 36, 48, 72 and 96.
eCRF: electronic case report form; IH: infantile haemangioma; RCT: randomized controlled trial; vs.: versus

The V00400SB 201 study was a double-blind, placebo-controlled, multicentre phase 2/3 approval study of propranolol with 5 study arms. Besides the placebo arm, there were 4 study arms, in which propranolol was investigated in different dosages. However, only the study arm in which propranolol was administered in compliance with the approval was included in the present assessment. After a titration phase this corresponds to daily administration of

3 mg/kg propranolol for 6 months (see Table 5). The other propranolol arms are not considered further.

Children aged 35 to 150 days with proliferating infantile haemangioma requiring systemic therapy were included in the study. Children with life- or function-threatening infantile haemangioma and children with ulcerated infantile haemangioma with pain and lack of response to simple wound care measures were excluded from participation in the study. According to the inclusion and exclusion criteria, the patients were also not allowed to have received pretreatment for their infantile haemangioma.

A total of 460 patients were randomly assigned to the 5 study arms, 102 of these patients to the relevant propranolol arm, and 55 patients to the placebo arm.

According to the Summary of Product Characteristics (SPC), propranolol is approved for the treatment of proliferating infantile haemangioma requiring systemic therapy. The therapeutic indication of propranolol is further specified as follows: life- or function-threatening haemangioma, ulcerated haemangioma with pain and/or lack of response to simple wound care measures, haemangioma with a risk of permanent scars or disfigurement [3]. Hence the population of the V00400SB 201 study could cover no more than a subpopulation of the therapeutic indication, i.e. patients with infantile haemangioma with a risk of permanent scars or disfigurement. It was further examined in the present benefit assessment which population was investigated in the V00400SB 201 study.

Since the study compared propranolol with placebo, it had to be examined additionally whether the administration of placebo in the V00400SB 201 study can be assessed as watchful waiting and whether watchful waiting is an option as ACT for the patient population investigated in the sense of individual treatment.

Based on an evaluation regarding content of the patient population investigated and of the regulatory documents [5,6], it was determined that only patients with infantile haemangioma with a risk of permanent scars or disfigurement were investigated in the V00400SB 201 study. Hence the V00400SB 201 study could only be used for assessing the added benefit in this subpopulation of the therapeutic indication of propranolol (see Section 2.7.2.4.1 of the full dossier assessment).

It was also inferred from the study requirements that the treatment in the placebo arm can be evaluated as watchful waiting. According to the study protocol, any drug or non-drug interventions for the treatment of infantile haemangioma were prohibited in both arms of the study (both in the treatment phase and during follow-up). The evolution of the target and non-target haemangioma was assessed by a physician at regular intervals (see Table 5). If it was considered to be medically necessary, study treatment could be discontinued and necessary interventions could be initiated. These requirements were overall considered to be sufficient in the framework of watchful waiting because close monitoring was planned for the early

detection of any complications and initiation of necessary interventions. Moreover, it was assumed for the patient population investigated that watchful waiting (here treatment with placebo) was suitable for them (for reasons see Section 2.7.2.4.1 of the full dossier assessment).

The primary outcome of the study was the complete/nearly complete resolution of the visible component of the target haemangioma at week 24 and was assessed on the basis of the comparison of photographs at the start of the study and at week 24 in a centralized evaluation by 2 independent readers. The company designated this outcome as "complete/nearly complete resolution of the haemangioma at week 24" in the dossier. However, the evaluation based on photographs only allows the assessment of the change in visible (superficial) components of the haemangioma. The designation of the company was therefore further specified in the present benefit assessment (see Section 2.7.2.4.3 of the full dossier assessment).

Patient-relevant secondary outcomes were the complete/nearly complete resolution of the target haemangioma at week 24 (evaluation by the investigator based on clinical examinations and photographic documentation), time to first sustained complete/nearly complete resolution of the target haemangioma, complete resolution of the non-target haemangioma, target haemangioma complications and AEs. All-cause mortality was recorded in the framework of the recording of SAEs.

The planned treatment phase of the study was 24 weeks (6 months). After its completion, the patients were observed for another 72 weeks (up to week 96). All outcomes were to be recorded until week 96.

However, the results at week 24 were used for all outcomes – except for all-cause mortality – in the present benefit assessment. For AEs, data up to 5 days after the last administration of the study medication were included in the analysis considered. The results at week 96 were used for all-cause mortality (see Section 2.7.2.4.3 of the full dossier assessment for the choice of analysis dates).

Table 6 shows the characteristics of the patients in the studies included.

Table 6: Characteristics of the study populations – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study characteristics category	Propranolol N = 102[a]	Placebo (watchful waiting) N = 55
V00400SB 201		
Age [days]: mean (SD)	102 (31)	104 (31)
35 - 90, n (%)	37 (36.6)	20 (36.4)
> 90, n (%)	64 (63.4)	35 (63.6)
Sex: [F/M], %	69/31	69/31
Location of target haemangioma, n (%)		
facial[b]	71 (70.3)	40 (72.7)
non-facial[c]	30 (29.7)	15 (27.3)
Morphological type, n (%)		
localized	91 (90.1)	48 (87.3)
segmental	5 (5.0)	2 (3.6)
indeterminate	5 (5.0)	5 (9.1)
Type of lesion, n (%)		
superficial component		
flat	9 (8.9)	4 (7.3)
raised	92 (91.1)	51 (92.7)
deep component present		
none	29 (28.7)	20 (36.4)
possible	16 (15.8)	10 (18.2)
clear	56 (55.4)	25 (45.5)
Secondary haemangioma, n (%)	ND[d]	ND[d]
Ethnicity, n (%)		
white	82 (81.2)[e]	46 (83.6)[e]
others	19 (18.8)[e,f]	9 (16.4)[e,g]
Treatment discontinuations, n (%)	14 (13.7)[h]	36 (65.5)

a: 102 patients were randomized. One patient received no study medication. The calculations are based on the ITT analysis (N = 101), unless otherwise stated.
b: This includes all haemangiomas that are above the skin with at least 10% of their surface.
c: The nappy area is excluded from this.
d: No clear data on the number of secondary haemangiomas (non-target haemangiomas) available.
e: Institute's calculation.
f: Others: black, Native Americans or Alaskans, Hawaiians, others, more than one ethnicity; Institute's calculation.
g: Others: Asian, others, unknown, more than one ethnicity; Institute's calculation.
h: This refers to 102 randomized patients.
F: female; ITT: intention to treat; M: male; N: number of randomized patients; n: number of patients in the category; ND: no data; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

The characteristics of the study population were largely comparable between the 2 relevant treatment arms. With regard to the type of lesion however, the presence of no deep component

was rarer in patients in the propranolol arm than in patients in the placebo arm (28.7% in the propranolol arm, and 36.4% in the placebo arm). Furthermore, the proportion of treatment discontinuations was notably lower in the propranolol arm (13.7%) than in the placebo arm (65.5%). This difference is also reflected in the information on treatment duration in the following Table 7.

Table 7 shows the median treatment duration of the patients. There was no information on the observation period available.

Table 7: Information on the course of the study – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study characteristics	**Propranolol N = 102[a]**	**Placebo (watchful waiting) N = 55**
V00400SB 201		
Median treatment duration [days], M [Q1, Q3]	168 [167, 169]	47 [21, 168]
Median observation period [days], M [Q1, Q3]	ND	ND
a: One patient received no study medication and was excluded from the ITT analysis. The calculations are based on the ITT analysis (N = 101). ITT: intention to treat; M: median; N: number of randomized patients; ND: no data; Q1: first quartile; Q3: third quartile; RCT: randomized controlled trial; vs.: versus		

The median treatment duration was 168 days in the propranolol arm and 47 days in the placebo arm. Hence the treatment durations differed notably between the study arms. No information on the actual observation period was available.

Table 8 shows the risk of bias at study level.

Table 8: Risk of bias at study level – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study	**Adequate random sequence generation**	**Allocation concealment**	**Blinding**		**Reporting independent of the results**	**No additional aspects**	**Risk of bias at study level**
			Patient	**Treating staff**			
V00400SB 201	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was rated as low for the V00400SB 201 study. This concurs with the company's assessment.

2.4 Results on added benefit

2.4.1 Outcomes included

The following patient-relevant outcomes were to be included in the present assessment (for reasons, see Section 2.7.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality (patients who died during the total study)
- Morbidity
  - complete/nearly complete resolution of the target haemangioma at week 24
  - complete/nearly complete resolution of the visible component of the target haemangioma at week 24
  - time to first sustained complete/nearly complete resolution of the target haemangioma
  - complete resolution of the non-target haemangioma
  - target haemangioma complications
- Health-related quality of life
- Adverse events
  - SAEs
  - treatment discontinuation due to AEs
  - bronchospasm (predefined list of Medical Dictionary for Regulatory Activities [MedDRA] terms)
  - infections and infestations (System Organ Class, SOC)
  - diarrhoea (Preferred Term, PT)

The choice of patient-relevant outcomes deviated from that of the company, which used further outcomes in its dossier (Module 4). The outcomes “complete/nearly complete resolution of the target haemangioma at week 24 (evaluation by the investigator)”, “complete resolution of the non-target haemangioma” and “target haemangioma complications” were additionally included in the present benefit assessment because they represent additional aspects of morbidity. The specific AEs (bronchospasm, infections and infestations, and diarrhoea) were chosen based on frequency and differences between the treatment groups in the V00400SB 201 study and under consideration of the patient relevance. Reasons for the choice of outcomes are given in Section 2.7.2.4.3 of the full dossier assessment.

Table 9 shows for which outcomes data were available in the study included.

Table 9: Matrix of outcomes – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study	Outcomes											
	All-cause mortality	Complete/nearly complete resolution of the target haemangioma at week 24[b]	Complete/nearly complete resolution of the visible component of the target haemangioma at week 24[c]	Time to first sustained complete/nearly complete resolution of the target haemangioma	Complete resolution of the non-target haemangioma[e]	Target haemangioma complications[f]	Health-related quality of life	SAEs	Discontinuation due to AEs	Bronchospasm[h]	Infections and infestations	Diarrhoea
V00400SB 201	Yes[a]	Yes	Yes	No[d]	No[d]	Yes[a]	No[g]	Yes[a]	Yes[a]	Yes[a]	Yes[a]	Yes[a]

a: Results are only interpretable in qualitative terms. See Section 2.7.2.4.3 of the full dossier assessment for reasons.
b: Evaluation by the investigator based on clinical examinations and photographic documentation.
c: Centralized evaluation based on the photographic documentation.
d: No evaluable data available. See Section 2.7.2.4.3 of the full dossier assessment for reasons.
e: Facial haemangiomas and haemangiomas in different localizations were considered.
f: Functional cardiac impairment, impairment of the eyes, obstruction of the visual axis, obstruction/stenosis of the airways, each of which with symptoms, as well as ulceration and bleeding requiring the initiation of therapeutic interventions were considered.
g: Outcome not recorded.
h: A list defined in the CSR including the HLT "bronchospasm and obstruction" and the following LLTs: apnoea, asthma, asthma bronchial, bronchial hyperactivity, bronchitis asthmatic, bronchospasm, shortness of breath, wheeze, and wheeze worsened.
AE: adverse event; CSR: clinical study report; HLT: MedDRA High Level Term; LLT: MedDRA Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The available documents contained data for all relevant outcomes except for health-related quality of life, which was not recorded in the V00400SB 201 study. For some outcomes however, the results were not evaluable. This applied to the outcomes "time to first sustained complete/nearly complete resolution of the target haemangioma" and "complete resolution of the non-target haemangioma". The results on all-cause mortality, target haemangioma complications and AEs were only interpretable in qualitative terms. For the outcomes "target haemangioma complications" and "AEs", this was justified by the fact that the treatment durations and consequently the observation periods between the study arms differed considerably due to the very large proportion of treatment discontinuations in the placebo arm (65.5% in the placebo arm versus 13.7% in the propranolol arm). For the outcome "all-cause mortality", the qualitative interpretation was caused by the different proportions of patients who participated in the follow-up observation (94% in the propranolol arm and 60% in the placebo arm). It was unclear how long the patients of both study arms were actually observed

for all-cause mortality. Additionally, for the outcome "complete resolution of the non-target haemangioma", the number of events could not be clearly derived according to the ITT principle from the information provided in the CSR (for detailed reasons see Section 2.7.2.4.3 of the full dossier assessment).

2.4.2 Risk of bias

Table 10 shows the risk of bias for these outcomes.

Table 10: Risk of bias at study and outcome level – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study	Study level	Outcomes											
		All-cause mortality	Complete/nearly complete resolution of the target haemangioma at week 24[b]	Complete/nearly complete resolution of the visible component of the target haemangioma at week 24[d]	Time to first sustained complete/nearly complete resolution of the target haemangioma	Complete resolution of the non-target haemangioma[f]	Target haemangioma complications[g]	Health-related quality of life	SAEs	Discontinuation due to AEs	Bronchospasm[j]	Infections and infestations	Diarrhoea
V00400SB 201	L	H[a]	H[c]	H[c]	-[e]	-[e]	H[h]	-[i]	H[h]	H[h]	H[h]	H[h]	H[h]

a: Results only interpretable in qualitative terms: Different proportions of the ITT population were included in the 96-week follow-up (propranolol: 94%, placebo: 60%).
b: Evaluation by the investigator based on clinical examinations and photographic documentation.
c: Due to the large difference between the study arms in the proportion of patients who were categorized as patients with treatment failure due to the early treatment discontinuation; see Section 2.4.3 and Section 2.7.2.4.3 of the full dossier assessment.
d: Centralized evaluation based on the photographic documentation.
e: No evaluable data available; see Section 2.7.2.4.3 of the full dossier assessment.
f: Facial haemangiomas and haemangiomas in different localizations were considered.
g: Functional cardiac impairment, impairment of the eyes, obstruction of the visual axis, obstruction/stenosis of the airways, each of which with symptoms, as well as ulceration and bleeding requiring the initiation of therapeutic interventions were considered.
h: Results only interpretable in qualitative terms because of the large difference in treatment duration and consequently the observation period between the study arms; see Section 2.7.2.4.3 of the full dossier assessment.
i: Outcome not recorded.
j: A list defined in the CSR including the HLT "bronchospasm and obstruction" and the following LLTs: apnoea, asthma, asthma bronchial, bronchial hyperactivity, bronchitis asthmatic, bronchospasm, shortness of breath, wheeze, and wheeze worsened.

AE: adverse event; CSR: clinical study report; H: high; HLT: MedDRA High Level Term; ITT: intention to treat; L: low; LLT: MedDRA Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; RCT: randomized controlled trial; SAE: serious adverse event; vs.: versus

The risk of bias was rated as high for all patient-relevant outcomes for which evaluable results were presented in the dossier. For the outcomes on resolution of the target haemangioma, target haemangioma complications and AES, the fact that notably more patients discontinued treatment and the study early in the placebo arm than in the propranolol arm was decisive for assessing the risk of bias as high.

For the outcomes on resolution of the target haemangioma, patients were categorized as patients with treatment failure after treatment discontinuation. Due to the large difference in the proportion of patients in this category, the results on these outcomes were highly biased.

For target haemangioma complications and AEs, bias occurred because the treatment periods differed greatly between the 2 study arms due to the difference in treatment discontinuation. The median treatment period resulting from the treatment discontinuation was 47 days in the placebo arm versus a median treatment period of 168 days of patients in the propranolol arm. Consequently, the observation periods and hence the times during which events were recorded differed greatly.

The results on the outcome “all-cause mortality” were also considered to be highly biased. The reason was that 95 out of 101 patients in the propranolol arm (94%) and only 33 out of 55 patients in the placebo arm (60%) participated in the follow-up until week 96. The observation period was overall unclear (see Section 2.7.2.4.2 of the full dossier assessment for detailed reasons).

There were no evaluable data for the outcomes “time to first sustained complete/nearly complete resolution of the target haemangioma” and “complete resolution of the non-target haemangioma”. Health-related quality of life was not investigated in the V00400SB 201 study. Therefore no outcome-specific assessment of the risk of bias of these outcomes was conducted.

The assessment of the risk of bias in the present benefit assessment deviates from the company’s assessment, which assessed the risk of bias as low for the outcomes included by the company. It also considered the results on the outcome “time to first sustained complete/nearly complete resolution of the target haemangioma” to be evaluable and used them for its assessment. Moreover, the company was inconsistent in its assessment of the risk of bias for the outcomes regarding harm, which it considered together and rated as having both a low and a high risk of bias in the dossier.

2.4.3 Results

Table 11 and Table 12 summarize the results on the comparison of propranolol versus placebo in patients with proliferating infantile haemangioma. Where necessary, the data from the company’s dossier were supplemented by the Institute’s calculations.

Table 11: Results (dichotomous outcomes) – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study **outcome category** **outcome** *type of analysis*	**Propranolol** **N**	**Patients with events n (%)**	**Placebo (watchful waiting)** **N**	**Patients with events n (%)**	**Propranolol vs. placebo (watchful waiting)** **RR [95% CI]; p-value**
V00400SB 201					
Mortality					
All-cause mortality	101	0 (0)	55	0 (0)	
Morbidity					
Complete/nearly complete resolution of the target haemangioma at week 24[a]					
Complete observation[b]	90	24 (26.7)	19	2 (10.5)	2.53 [0.65; 9.82]; 0.145[c]
Imputation strategy 1[d]	101	- (24.9)	55	- (10.5)	2.37 [0.61; 9.23]; 0.214
Imputation strategy 2[e]	101	- (26.7)	55	- (3.6)	7.33 [0.71; 76.09]; 0.095
Imputation strategy 3[f]	101	- (23.8)	55	- (3.6)	6.53 [0.63; 68.07]; 0.117
Complete/nearly complete resolution of the visible component of the target haemangioma at week 24[g]					
Per protocol[h]	93	56 (60.2)	53	1 (1.9)	31.91 [4,55; 223.96][i]; < 0.001[c]
Imputation strategy 4[j]	101	62 (61.4)	55	15 (27.3)	2.25 [1.42; 3.56][i]; < 0.001[c]
Imputation strategy 3[f]	101	61 (60.4)	55	2 (3.6)	16.61 [4.22; 65.34]; < 0.001[c]
Target haemangioma complications (functional impairment, ulceration and bleeding[k])	Results only interpretable in qualitative terms[l]				
Complete resolution of the non-target haemangioma (facial)	No evaluable data[m]				
Complete resolution of the non-target haemangioma (non-facial)	No evaluable data[m]				
Adverse events					
AEs	Results only interpretable in qualitative terms[l]				
Discontinuation due to AEs	Results only interpretable in qualitative terms[l]				
SAEs	Results only interpretable in qualitative terms[l]				
Bronchospasm[n]	Results only interpretable in qualitative terms[l]				
Infections and infestations (SOC)	Results only interpretable in qualitative terms[l]				
Diarrhoea (PT)	Results only interpretable in qualitative terms[l]				

(continued)

Table 11: Results (dichotomous outcomes) – RCT, direct comparison: propranolol vs. placebo (watchful waiting) (continued)

a: Evaluation by the investigator based on clinical examinations and photographic documentation.
b: The number of patients does not consider treatment discontinuations and protocol violations (propranolol: 11/101 [10.9%], placebo: 36/55 [65.5%]). This analysis is only presented as additional information.
c: Institute's calculation, unconditional exact test (CSZ method according to [7]).
d: Institute's calculation: For patients who discontinued therapy, it was assumed in both treatment arms that they reach the outcome with the probability with which those patients of the control group reach it who did not discontinue therapy. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]); p-values asymptotic.
e: Institute's calculation: For patients who discontinued therapy, it was assumed in the intervention arm that they reach the outcome with the probability with which those patients of the intervention arm reach it who did not discontinue therapy. For patients in the control it was assumed that they do not reach the outcome. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]); p-values asymptotic.
f: Institute's calculation: For patients who discontinued treatment, it was assumed in both treatment arms that they do not reach the outcome. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]); p-values asymptotic.
g: Centralized evaluation based on the photographic documentation.
h: Analysis based on the per-protocol population (sensitivity analysis of the company).
i: Institute's calculation; a correction of variance could not be conducted because no data on the number of imputed values were available.
j: Treatment success defined as complete/nearly complete resolution of the target haemangioma at week 24 was randomly assigned to 50% of the patients without confirmation of worsening or stabilization of the target haemangioma on the last documented study visit (sensitivity analysis of the company).
k: Functional cardiac impairment, impairment of the eyes, obstruction of the visual axis, obstruction/stenosis of the airways, each of which with symptoms, as well as ulceration and bleeding requiring the initiation of therapeutic interventions were considered.
l: See Appendix B, Table 23 of the full dossier assessment for the presentation of the naive proportions of patients with events.
m: The data presented in the CSR are not interpretable; see Section 2.7.2.4.3 of the full dossier assessment.
n: A list defined in the CSR including the HLT "bronchospasm and obstruction" and the following LLTs: apnoea, asthma, asthma bronchial, bronchial hyperactivity, bronchitis asthmatic, bronchospasm, shortness of breath, wheeze, and wheeze worsened.

AE: adverse event; CI: confidence interval; CSR: clinical study report; CSZ: convexity, symmetry, z score; HLT: MedDRA High Level Term; LLT: MedDRA Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; N: Number of analysed patients; n: number of patients with event; PT: MedDRA Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: MedDRA System Organ Class; vs.: versus

Table 12: Results (time to event) – RCT, direct comparison: propranolol vs. placebo (watchful waiting)

Study outcome category outcome	Propranolol N	Propranolol Median time to event in months [95% CI]	Placebo (watchful waiting) N	Placebo (watchful waiting) Median time to event in months [95% CI]	Propranolol vs. placebo (watchful waiting) HR [95% CI]	 p-value
V00400SB 201						
Morbidity						
Time to first sustained complete/nearly complete resolution of the target haemangioma						
				No evaluable data[a]		

a: The data presented in the CSR are not interpretable; see Section 2.7.2.4.3 of the full dossier assessment.
CI: confidence interval; CSR: clinical study report; HR: hazard ratio; N: number of analysed patients: RCT: randomized controlled trial; vs.: versus

Only one relevant study was available for the assessment of propranolol. The V00400SB 201 study did not meet the particular requirements placed on the derivation of proof of an added benefit from a single study [1]. Hence, at most "indications" could be derived from the data.

Mortality

All-cause mortality

No deaths occurred in the total observation period (96 weeks). However, different proportions of patients of the ITT population were included in the follow-up (94% in the propranolol arm and 60% in the placebo arm). It could only be concluded for this outcome that the data presented showed no greater harm from propranolol. Hence an added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to the outcome "all-cause mortality" is not proven.

Overall, this concurs with the assessment of the company, which also derived no added benefit for this outcome category.

Morbidity

Complete/nearly complete resolution of the target haemangioma at week 24

The results for the outcome "complete/nearly complete resolution of the target haemangioma at week 24 (evaluation by the investigator based on clinical examinations and photographic documentation)" resulted in no statistically significant result from the analysis of the completely observed patients. All patients who did not discontinue treatment or the study early and who committed no other serious protocol violations were included in the analysis. This analysis, which violated the ITT principle because of the large proportion of patients who were not considered, was only presented as additional information. Since it was unclear whether the patients who were not considered in the analysis would have reached complete/nearly complete resolution of the target haemangioma, 3 sensitivity analyses

regarding the imputation of missing values were conducted for this outcome. This examined how different scenarios for the imputation of missing values influence the treatment effect of propranolol. This applied to 11 of 101 patients (10.9%) in the propranolol, and to 36 of 55 patients (65.5%) in the placebo arm.

In imputation strategy 1, it was assumed in both treatment arms that patients who discontinued therapy reached the outcome with the probability with which those patients of the control group reached it who did not discontinue therapy. The placebo arm was favoured in this imputation strategy.

In imputation strategy 2, for patients who discontinued therapy, it was assumed in the intervention arm that they reached the outcome with the probability with which those patients of the intervention arm reached it who did not discontinue therapy. For patients in the control it was assumed that they do not reach the outcome. This strategy was used as an approximation to the expected clinical course without further spontaneous remissions. The propranolol arm was favoured in this imputation strategy.

In imputation strategy 3, it was assumed for patients in both treatment arms who discontinued therapy that they did not reach the outcome. The placebo arm was favoured in this imputation strategy because of the higher rates of discontinuation.

In all 3 imputation strategies, the variances were adapted according to the data-set re-sizing approach (approach W3 in [8]).

A numerical advantage of propranolol was seen both in the analysis using the completely observed cases and in the 3 sensitivity analyses, even in the analyses in which the missing values were imputed to the disadvantage of propranolol (imputation strategies 1 and 3). However, there was no statistically significant result in any of the 3 sensitivity analyses. Hence no added benefit of propranolol in comparison with watchful waiting (with administration of placebo) was derived for the outcome “complete/nearly complete resolution of the target haemangioma at week 24 (evaluation by the investigator)”.

The company did not use this outcome in its assessment.

Complete/nearly complete resolution of the visible component of the target haemangioma at week 24

The results of the per protocol analysis showed that statistically significantly more patients reached complete/nearly complete resolution of the target haemangioma at week 24 in the propranolol arm than in the placebo arm. Patients who discontinued treatment early and those who were taking prohibited medication were recorded in this analysis as patients with treatment failure.

Sensitivity analyses were conducted to examine whether deviating scenarios for the imputation of missing values raise important doubts about the notable treatment effect in favour of propranolol.

In the first sensitivity analysis (imputation strategy 4), 50% of the patients in both treatment arms who discontinued treatment early for other reasons than intolerance and for whom no stabilization or worsening could be determined in the last documented assessment were considered to be patients who responded to treatment. Due to the observed success rates, this approach favours the placebo arm.

In the second analysis (imputation strategy 3), all patients who discontinued treatment were categorized as patients with treatment failure. As a result, the event rate was comparable with the per-protocol analysis in the propranolol arm. In the placebo arm, this strategy corresponded to the expected clinical course without further spontaneous remissions.

The company conducted no correction of variance with regard to the missing values for treatment discontinuations for any of the 3 analyses. This could also not be conducted subsequently because no data on the number of imputed values were available.

The results of both imputation strategies (3 and 4) showed that no doubts are raised about the magnitude the resulting effect from the per-protocol analysis because of the unequal proportion of missing values in the 2 treatment arms. All analyses showed an effect of a major extent in favour of propranolol. Overall, the certainty of conclusions for the outcome "complete/nearly complete resolution of the visible component of the target haemangioma" was not downgraded because of this despite the high risk of bias. Hence an indication of an added benefit of propranolol in comparison with watchful waiting (with administration of placebo) was derived for this outcome.

This concurs with the company's assessment, which also derived an indication of added benefit based on this outcome.

Time to first sustained complete/nearly complete resolution of the target haemangioma

The results for the outcome "time to first sustained complete/nearly complete resolution of the target haemangioma" were considered to be not interpretable. Due to the notable difference in treatment duration between the study arms (median treatment duration of 168 days in the propranolol arm, and of 47 days in the placebo arm) and the associated high informative bias, there were no available data (see Section 2.7.2.4.3 of the full dossier assessment).

This deviates from the company's assessment, which derived an indication of added benefit based on this outcome.

Target haemangioma complications

For the outcome "target haemangioma complications (functional impairment, ulceration and bleeding)", the results were only interpreted in qualitative terms due to the notable differences

in treatment duration between the study arms (see Section 2.7.2.4.3 of the full dossier assessment). Based on the naive proportions of patients with event, there was no statistically significant difference between the treatment arms with regard to this outcome. It could only be concluded for this outcome that the data presented showed no greater or lesser benefit despite the bias to the disadvantage of propranolol. Hence the added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to target haemangioma complications is not proven.

The company did not use this outcome in its assessment.

Complete resolution of the non-target haemangioma

There were no evaluable data for the outcomes "complete resolution of the non-target haemangioma (facial)" and "complete resolution of the non-target haemangioma (non-facial)" because the number of events could not be clearly derived according to the ITT principle from the information provided in the CSR. Hence the added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to the complete resolution of the non-target haemangioma is not proven.

The company did not use this outcome in its assessment.

Health-related quality of life

Health-related quality of life was not investigated in the study. An added benefit of propranolol in comparison with watchful waiting (with administration of placebo) with regard to health-related quality of life is not proven.

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

Adverse events

The overall rates of AEs, the AEs that most commonly occurred in the V00400SB 201 study, SAEs and discontinuations due to AEs are presented in Appendix A of the full dossier assessment. The results for all outcomes regarding harm were only interpreted in qualitative terms due to the notable differences in treatment duration between the study arms (see Section 2.7.2.4.3 of the full dossier assessment). Appendix B of the full dossier assessment shows the effects on the basis of the naive proportions of AEs to support the qualitative interpretation of the data.

Serious adverse events

Based on the naive proportions of patients with event, there was no statistically significant difference between the treatment arms with regard to the outcome "SAEs". It could only be concluded for this outcome that the data presented showed no greater harm despite the bias to the disadvantage of propranolol. Hence greater or lesser harm from propranolol in comparison with watchful waiting (with administration of placebo) with regard to SAEs is not proven.

Discontinuation due to adverse events

Based on the naive proportions of patients with event, there was a statistically significant difference between the treatment groups in favour of propranolol with regard to the outcome "discontinuation due to AEs". However, on further consideration of the results leading to discontinuation due to AEs it can be concluded that this outcome also included events that were attributable to worsening of the haemangioma or lack of efficacy of the study medications. Overall, a conclusion could be derived that the available data showed no greater harm from propranolol regarding discontinuation due to AEs. Greater or lesser harm from propranolol in comparison with watchful waiting (with administration of placebo) is not proven for this outcome.

Bronchospasm

Based on the naive proportions of patients with event, there was no statistically significant difference between the treatment arms with regard to the outcome "bronchospasm". It could only be concluded for this outcome that the data presented showed no greater harm despite the bias to the disadvantage of propranolol. Hence greater or lesser harm from propranolol in comparison with watchful waiting (with administration of placebo) with regard to bronchospasm is not proven.

Infections and infestations (SOC) and diarrhoea (PT)

Based on the naive proportions of patients with event, there was a statistically significant effect to the disadvantage of propranolol for the outcomes "infections and infestations" and "diarrhoea". Also under consideration of the direction of the bias to the disadvantage of propranolol, potential harm from propranolol cannot be completely excluded for these outcomes.

The company presented the results on the individual operationalizations of the complex "adverse events" using the naive proportions. Overall, the company derived no greater or lesser harm from propranolol from this.

2.4.4 Subgroups and other effect modifiers

The company presented subgroup analyses by age, sex, and localization of the haemangioma for the outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24". It presented no interaction tests. Due to the bias as a consequence of the large difference between the study arms in the proportion of patients who were categorized as patients with treatment failure due to the early treatment discontinuation, the magnitude of the bias may differ in the subgroups. Statistically significant results from interaction tests may be caused by this bias alone. Hence results from the interaction tests would have been regarded to be not interpretable and not have been considered in the present benefit assessment. Overall, the subgroup analyses presented by the company in the dossier are therefore not evaluable (see Section 2.7.2.2 of the full dossier assessment).

2.5 Extent and probability of added benefit

The derivation of extent and probability of added benefit is presented below at outcome level, 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 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.

2.5.1 Assessment of added benefit at outcome level

The data presented in Section 2.4 resulted in an indication of an added benefit for the outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24".

Due to the notable differences in treatment durations and consequent observation periods between the study arms, the results on the outcome "target haemangioma complications" as well as "all-cause mortality" and "AEs" could only be interpreted in qualitative terms. A statistically significant effect to the disadvantage of propranolol was shown for the outcomes regarding harm "infections and infestations" and "diarrhoea". Under consideration of the direction of the bias it was overall unclear whether the observed effects were really based on greater harm or caused by the bias. Greater harm from propranolol regarding infections and infestations as well as diarrhoea could not be excluded.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: propranolol vs. watchful waiting (with administration of placebo; patients with proliferating infantile haemangioma with a risk of permanent scars or disfigurement)

Outcome category **outcome**	**Propranolol vs. placebo (watchful waiting)** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Mortality		
All-cause mortality	0% vs. 0%	Lesser benefit/added benefit not proven
Morbidity		
Complete/nearly complete resolution of the target haemangioma at week 24[c]	**Complete observation**[d] 26.7% vs. 10.5% RR: 2.53 [0.65; 9.82]; 0.145[e] **Imputation strategy 1**[f] 24.9% vs. 10.5% RR: 2.37 [0.61; 9.23]; 0.214 **Imputation strategy 2**[g] 26.7% vs. 3.6% RR: 7.33 [0.71; 76.09]; 0.095 **Imputation strategy 3**[h] 23.8% vs. 3.6% RR: 6.53 [0.63; 68.07]; 0.117	Added benefit not proven
Complete/nearly complete resolution of the visible component of the target haemangioma at week 24[i]	**Per protocol**[j] 60.2% vs. 1.9% RR: 31.91 [4.55; 223.96][k]; RR[l]: 0.03 [0.00; 0.22] < 0.001[e] **Imputation strategy 4**[m] 61.4% vs. 27.3% RR: 2.25 [1.42; 3.56][k]; RR[l]: 0.44 [0.28; 0.70]; < 0.001[e] **Imputation strategy 3**[h] 60.4% vs. 3.6% RR: 16.61 [4.22; 65.34]; RR[l]: 0.06 [0.02; 0.24]; < 0.001[e] probability: “indication”	Outcome category: serious/severe symptoms added benefit, extent: “major”

(continued)

Table 13: Extent of added benefit at outcome level: propranolol vs. watchful waiting (with administration of placebo; patients with proliferating infantile haemangioma with a risk of permanent scars or disfigurement) (continued)

Outcome category **outcome**	**Propranolol vs. placebo (watchful waiting)** **effect estimate [95% CI]** **p-value** **probability**[a]	**Derivation of extent**[b]
Time to first sustained complete/nearly complete resolution of the target haemangioma	No evaluable data available	
Target haemangioma complications (functional impairment, ulceration and bleeding[n])	Qualitative interpretation on the basis of the naive proportions of the patients with target haemangioma complications[c]	Added benefit not proven
Complete resolution of the non-target haemangioma[p]	No evaluable data available	
Health-related quality of life		
	Outcome not investigated	
Adverse events		
Discontinuation due to AEs	Qualitative interpretation on the basis of the naive proportions of the patients with AEs[o]	Outcome category: non-serious/non-severe AEs $CI_u > 0.9$ Greater/lesser harm not proven
SAEs	Qualitative interpretation on the basis of the naive proportions of the patients with AEs[o]	Greater/lesser harm not proven
Bronchospasm[q]	Qualitative interpretation on the basis of the naive proportions of the patients with AEs[o]	Greater/lesser harm not proven
Infections and infestations (SOC)	Qualitative interpretation on the basis of the naive proportions of the patients with AEs[o]	Not evaluable due to bias; greater harm cannot be excluded
Diarrhoea (PT)	Qualitative interpretation on the basis of the naive proportions of the patients with AEs[o]	Not evaluable due to bias; greater harm cannot be excluded

(continued)

Table 13: Extent of added benefit at outcome level: propranolol vs. watchful waiting (with administration of placebo; patients with proliferating infantile haemangioma with a risk of permanent scars or disfigurement) (continued)

a: Probability provided if statistically significant differences were present.
b: Estimations of effect size are made depending on the outcome category with different limits based on the CI_u.
c: Evaluation by the investigator based on clinical examinations and photographic documentation.
d: The number of patients does not consider treatment discontinuations and protocol violations (propranolol: 11/101 [10.9%], placebo: 36/55 [65.5%]). This analysis is only presented as additional information.
e: Institute's calculation, unconditional exact test (CSZ method according to [7]).
f: Institute's calculation: For patients who discontinued therapy, it was assumed in both treatment arms that they reach the outcome with the probability with which those patients of the control group reach it who did not discontinue therapy. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]); p-values asymptotic.
g: Institute's calculation: For patients who discontinued therapy, it was assumed in the intervention arm that they reach the outcome with the probability with which those patients of the intervention arm reach it who did not discontinue therapy. For patients in the control it was assumed that they do not reach the outcome. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]); p-values asymptotic.
h: Institute's calculation: For patients who discontinued treatment, it was assumed in both treatment arms that they do not reach the outcome. The variances were adapted according to the data-set re-sizing approach (approach W3 in [8]); p-values asymptotic.
i: Centralized evaluation based on the photographic documentation.
j: Analysis based on the per-protocol population (sensitivity analysis of the company).
k: Institute's calculation; a correction of variance could not be conducted because no data on the number of imputed values were available.
l: Institute's calculation: reversed direction of effect to enable direct use of limits to derive added benefit.
m: Treatment success defined as complete/nearly complete resolution of the target haemangioma at week 24 was randomly assigned to 50% of the patients without confirmation of worsening or stabilization of the target haemangioma on the last documented study visit (sensitivity analysis of the company).
n: Functional cardiac impairment, impairment of the eyes, obstruction of the visual axis, obstruction/stenosis of the airways, each of which with symptoms, as well as ulceration and bleeding requiring the initiation of therapeutic interventions were considered.
o: The naive proportions of the patients with events are presented in Appendix B, Table 23, of the full dossier assessment.
p: Facial haemangiomas and haemangiomas in different localizations were considered.
q: A list defined in the CSR including the HLT "bronchospasm and obstruction" and the following LLTs: apnoea, asthma, asthma bronchial, bronchial hyperactivity, bronchitis asthmatic, bronchospasm, shortness of breath, wheeze, and wheeze worsened.

AE: adverse event; CI: confidence interval; CI_u: upper limit of CI; CSR: clinical study report; CSZ: convexity, symmetry, z score; HLT: MedDRA High Level Term; LLT: MedDRA Lowest Level Term; MedDRA: Medical Dictionary for Regulatory Activities; PT: MedDRA Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: MedDRA System Organ Class; vs.: versus

2.5.2 Overall conclusion on added benefit

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

Table 14: Patients with proliferating infantile haemangioma with a risk of permanent scars or disfigurement: positive and negative effects from the assessment of propranolol in comparison with watchful waiting (with administration of placebo)

Positive effects	**Negative effects**
Indication of added benefit – extent: "major" (serious/severe symptoms: complete/nearly complete resolution of the visible component of the target haemangioma at week 24)	An adequate assessment of infections and infestations as well as diarrhoea was not possible because of uncertainty in the assessment of the effects. Greater harm is not excluded.

Based on the available results, a positive effect (indication) of propranolol remains for the outcome category "serious/severe symptoms" (outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24").

On the negative side, only a qualitative interpretation of the results could be conducted because of a notable difference in treatment duration between the study arms. There was a statistically significant effect to the disadvantage of propranolol for the outcomes "diarrhoea" and "infections and infestations". Despite the direction of the bias (to the disadvantage of propranolol), potential harm from propranolol could not be completely excluded.

The available results, however, did not provide signs of harm due to diarrhoea and infections and infestations in a magnitude that would justify downgrading the added benefit of propranolol. This is particularly justified by the size of the effect regarding benefit for the outcome "complete/nearly complete resolution of the visible component of the target haemangioma at week 24". At the same time, most AEs were classified as non-serious. Moreover, the ratio of occurrence of diarrhoea and infections and infestations in the study arms roughly corresponded to the ratio of treatment duration in the 2 relevant study arms.

A conclusion on the added benefit of propranolol can be derived from the V00400SB 201 study for the subpopulation of patients with proliferating infantile haemangioma requiring systemic therapy with a risk of permanent scars or disfigurement for whom watchful waiting in the sense of individual treatment is an option as ACT. Overall, there is an indication of major added benefit of propranolol versus the ACT watchful waiting for the patients of this subpopulation.

The result of the assessment of the added benefit of propranolol in comparison with the ACT is summarized in Table 15.

Table 15: Propranolol – extent and probability of added benefit

Therapeutic indication	ACT[a]	Extent and probability of added benefit
Treatment of proliferating infantile haemangioma requiring systemic therapy:		
Life- or function-threatening haemangioma	Individual treatment. The specifications of the respective SPCs of the drugs used for treatment are to be taken into account.	Added benefit not proven
Ulcerated haemangioma with pain and/or lack of response to simple wound care measures		Added benefit not proven
Haemangioma with a risk of permanent scars or disfigurement		Indication of a major added benefit[b]
a: Presentation of the ACT specified by the G-BA. b: For patients in whom watchful waiting in the sense of individual treatment is an option as ACT. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This deviates from the company's approach, which derived an indication of a major added benefit for the total therapeutic indication of propranolol.

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

2.6 List of included studies

Pierre Fabre Dermatologie. A randomised, controlled, multidose, multicentre, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of ropranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind) [online]. In: EU Clinical Trials Register. [Accessed: 18 September 2014]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2009-013262-84.

Pierre Fabre Dermatologie. A randomized, controlled, multidose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind): study V00400 SB 2 01; clinical study report for primary analysis up to week 24 [unpublished]. 2012.

Pierre Fabre Dermatologie. A randomized, controlled, multidose, multicenter, adaptive phase II/III study in infants with proliferating infantile hemangiomas requiring systemic therapy to compare four regimens of propranolol (1 or 3 mg/kg/day for 3 or 6 months) to placebo (double blind): study V00400 SB 2 01; clinical study report; full report up to week 96 [unpublished]. 2014.

Pierre Fabre Dermatology. Study to demonstrate the efficacy and safety of propranolol oral solution in infants with proliferating infantile hemangiomas requiring systemic therapy: full text view [online]. In: Clinicaltrials.gov. 21 May 2014 [accessed: 25 September 2014]. URL: http://ClinicalTrials.gov/show/NCT01056341.

Pierre Fabre Dermatology. Study to demonstrate the efficacy and safety of propranolol oral solution in infants with proliferating infantile hemangiomas requiring systemic therapy: study results [online]. In: Clinicaltrials.gov. 21 May 2014 [accessed: 25 September 2014]. URL: http://clinicaltrials.gov/ct2/show/results/NCT01056341.

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Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/de/projekte-ergebnisse/projekte/arzneimittelbewertung/a14-29-propranolol-nutzenbewertung-gemaess-35a-sgb-v-dossierbewertung.6346.html.