IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Sonidegib (basal cell carcinoma) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Sonidegib (Basalzellkarzinom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 9 May 2018). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

Richard F. Schlenk, NCT Trial Center, National Center for Tumor Diseases, Heidelberg, Germany

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IQWiG employees involved in the dossier assessment:

- Michael Köhler
- Elena Bardach
- Judith Gibbert
- Charlotte Guddat
- Marco Knelangen
- Min Ripoll
- Cornelia Rüdig
- Volker Vervölgyi

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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
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
laBCC	locally advanced basal cell carcinoma
mBCC	metastatic basal cell carcinoma
pEAS	primary efficacy analysis set
RCT	randomized controlled trial
SAE	serious adverse event
SF-36	Short Form (36) Health Survey
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book 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 sonidegib. 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 14 February 2018.

Research question

The aim of the present report was the assessment of the added benefit of sonidegib in patients with locally advanced basal cell carcinoma (laBCC) who are not amenable to curative surgery or radiation therapy.

The assessment of the added benefit was conducted in comparison with the appropriate comparator therapy (ACT) specified by the G-BA. This ACT is shown in Table 2.

Table 2: Research questions of the benefit assessment of sonidegib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy	**Vismodegib** or best supportive care[b]

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: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

In its dossier, the company chose vismodegib as ACT. This approach was followed.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Studies included by the company

The company presented no randomized controlled trials (RCTs) of direct comparison for the assessment of the added benefit of sonidegib versus the ACT. Since, according to the company, there were no relevant RCTs comparing sonidegib with the ACT or another treatment, the company compared individual arms of different studies without adjustment using a common comparator.

On the sonidegib side, the company presented the RCT BOLT. This study compared 2 dosages of sonidegib with each other (200 mg/day versus 800 mg/day). It included adult patients with laBCC who were not amenable to curative surgery, radiation therapy or other local treatments, as well as patients with metastatic basal cell carcinoma (mBCC). Since sonidegib is approved at a dosage of 200 mg/day, the company only considered laBCC patients from the 200 mg arm of the study in its dossier. This subpopulation comprised 66 patients. Regarding population, intervention and outcomes, the study concurred with the inclusion criteria of the present benefit assessment.

On the side of the ACT vismodegib, the company included the study ERIVANCE. This was a single-arm study with adult patients with laBCC or mBCC. The company presented results for the laBCC population, which comprised 71 patients. In the study, vismodegib was administered in a dosage of 150 mg/day. The ERIVANCE study had already been assessed in the benefit assessment procedure on vismodegib [3-5]. Regarding population, intervention and outcomes, it also concurred with the inclusion criteria of the present benefit assessment.

In the framework of the check of completeness of the study pool, 3 additional single-arm studies on vismodegib were identified in the search in trial registries. Due to their patient population, intervention and outcomes, these studies (STEVIE [MO25616], SHH4811g [US-EAP], SHH3925g) were principally relevant for the benefit assessment. The company did not include these studies in its benefit assessment. In particular, the exclusion of the STEVIE study with 1119 laBCC patients was inadequate. Hence, the study pool of the company was incomplete. An added benefit of sonidegib is therefore not proven. This is of particular importance as the consideration of the STEVE study causes a relevant change in the results on overall survival (the outcome on which the company based its added benefit), and also on other patient-relevant outcomes.

Assessment of the evidence presented by the company

The company’s assessment of the added benefit was exclusively based on the comparison of individual arms from 2 different studies. Results from comparisons of individual study arms are generally very uncertain, so that conclusions on the added benefit can only be derived in the presence of large effects.

For the comparison of the studies BOLT and ERIVANCE, the company described statistically significant differences in several outcomes (overall survival, serious adverse events [SAEs], muscle spasms, weight loss). The company ignored the results of the STEVIE study on vismodegib, however. In several outcomes, this study showed numerically smaller differences in comparison with the BOLT study than those shown between the studies BOLT and ERIVANCE. As a result, a joint consideration of both vismodegib studies may show no advantage of sonidegib.

Even under consideration of the studies BOLT and ERIVANCE alone, the observed effects were not sufficiently large that they could not be caused by bias alone. Hence, the company

overall presented no data in its dossier that are suitable for the assessment of the added benefit of sonidegib in laBCC. Consequently, there was no hint of an added benefit of sonidegib in comparison with the ACT. An added benefit is therefore not proven.

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

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

No suitable data were available for the assessment of the added benefit of sonidegib in adult patients with laBCC.

Table 3 presents a summary of the probability and extent of the added benefit of sonidegib.

Table 3: Sonidegib – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy	**Vismodegib** or best supportive care[b]	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: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was the assessment of the added benefit of sonidegib in comparison with the ACT in patients with laBCC who are not amenable to curative surgery or radiation therapy.

This resulted in one research question for the benefit assessment, for which the G-BA specified the ACT presented in Table 4.

[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 4: Research questions of the benefit assessment of sonidegib

Research question	Therapeutic indication	ACT[a]
1	Adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy	**Vismodegib** or best supportive care[b]

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: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The company chose vismodegib as ACT in its dossier, thus following the G-BA's specification. This approach was followed.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

2.3 Information retrieval and study pool

2.3.1 Information retrieval

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 sonidegib (status: 15 December 2017)
- bibliographical literature search on sonidegib (last search on 17 January 2018)
- search in trial registries for studies on sonidegib (last search on 7 December 2017)
- bibliographical literature search on the ACT (last search on 17 January 2018)
- search in trial registries for studies on the ACT (last search on 29 December 2017)

To check the completeness of the study pool:

- search in trial registries for studies on sonidegib (last search on 1 March 2018)
- search in trial registries for studies on the ACT (last search on 1 March 2018)

In its information retrieval, the company identified no studies on the direct comparison of sonidegib versus the ACT. It therefore searched for further investigations on sonidegib as well as on the ACT. The search produced the RCT BOLT on the sonidegib side, and the single-arm ERIVANCE study on the vismodegib side.

The check of the completeness of the study pool also identified no study of direct comparison on sonidegib in comparison with the ACT. However, it identified further potentially relevant studies on the ACT, which were not included by the company. These are described in Section 2.3.2 of the present benefit assessment.

The data presented by the company were unsuitable to derive an added benefit of sonidegib in comparison with the ACT. This is justified below.

2.3.2 Evidence provided by the company

The company presented no RCTs of direct comparison for the assessment of the added benefit of sonidegib versus the ACT. Since, according to the company, there were no relevant RCTs comparing sonidegib with the ACT or another treatment, the company compared individual arms of different studies without adjustment using a common comparator.

Studies on sonidegib

On the sonidegib side, the company presented the RCT BOLT [6-9]. This study compared 2 dosages of sonidegib with each other (200 mg/day versus 800 mg/day). It included adult patients with laBCC who were not amenable to curative surgery, radiation therapy or other local treatments, as well as patients with mBCC. Sonidegib is not approved for the latter patient group. Since, according to the Summary of Product Characteristics (SPC), sonidegib is administered at a dosage of 200 mg/day [10], the company only considered laBCC patients from the 200 mg arm of the study in its dossier. This subpopulation principally concurred with the inclusion criteria of the present benefit assessment and comprised 66 patients.

Primary outcome of the study was the objective response rate. Secondary outcomes included overall survival, progression-free survival, duration of response, time to tumour response, symptoms, health-related quality of life, and adverse events (AEs), among others. Results on a total of 5 data cut-offs were available for the study. The company used the results of the 2 most recent data cut-offs from July 2015 (48 months after the start of the study) and July 2016 (60 months after the start of the study) for the assessment of the added benefit.

Tables on the characteristics of the BOLT study can be found in Appendix A of the full dossier assessment.

Study on vismodegib included by the company

The company included the ERIVANCE study for vismodegib [11-14]. This was a single-arm study with adult patients with laBCC or mBCC. The company presented results for the laBCC population, which comprised 71 patients. In the study, vismodegib was administered in a dosage of 150 mg/day. This concurs with the requirements of the SPC [15].

Primary outcome of this study was also the objective response rate. Secondary outcomes included overall survival, progression-free survival, symptoms, health-related quality of life, and AEs, among others. There were 6 data cut-offs for this study [5], of which the company

used the last data cut-off from 30 May 2013 (51 months after the start of the study) for the assessment of the added benefit.

The ERIVANCE study had already been assessed in the benefit assessment procedure on vismodegib [3-5]. Regarding population, intervention and outcomes, it also concurred with the inclusion criteria of the present benefit assessment.

Tables on the characteristics of the ERIVANCE study can be found in Appendix A of the full dossier assessment.

Further relevant studies not included by the company

In the framework of the check of completeness of the study pool, 3 additional single-arm studies on vismodegib were identified in the search in trial registries. Due to their patient population, intervention and outcomes, these studies were principally relevant for the benefit assessment. These were the studies STEVIE (MO25616) [16,17], SHH4811g (US-EAP) [14,18] and SHH3925g [19]. These studies had already been rated as relevant in the benefit assessments on vismodegib in laBCC patients [3,4].

The studies STEVIE and SHH4811g were single-arm studies with adult patients with laBCC and mBCC who received 150 mg/day vismodegib. The STEVIE study recorded overall survival, objective response rate, health-related quality of life and AEs, among others; the SHH4811g study recorded objective response rates and side effects. In the STEVIE study, 1119 patients with laBCC were included in the analysis [16]. The SHH4811g study included 62 patients [14]. The SHH3925g study included only 2 patients with laBCC [5]. The patient numbers show that particularly the STEVIE study can have a decisive influence on the result of a comparison of individual study arms. The result of the company's assessment can therefore be highly biased due to the missing STEVIE study (see Section 2.3.3). Against this background, the fact that the 2 smaller studies were missing is of less importance.

The company cited the STEVIE study in Module 4A of its dossier, but only in Section 4.5.2 (Reasons for the presentation of non-randomized comparative studies and further investigations), and not under the included studies. Hence, the study pool of the company was incomplete. An added benefit of sonidegib is not proven for this reason alone. This is of particular importance as the consideration of the STEVE study causes a relevant change in the results on overall survival (the outcome on which the company based its added benefit), and also on other patient-relevant outcomes (see below).

The company excluded the STEVIE study with the justification that the studies STEVIE and BOLT were less compatible with regard to the data cut-offs than ERIVANCE and BOLT. Considering the data cut-offs, this is not comprehensible. For its comparison, the company used the data cut-offs at months 48 and 60 after the start of the study for the BOLT study, and the data cut-off at month 51 for the ERIVANCE study. The reference time point is the start of inclusion of the patients. However, the company did not describe why the used data cut-offs of

the studies BOLT and ERIVANCE were sufficiently similar, whereas the ones of BOLT and STEVIE were not. It can be inferred from the current 2017 publication on the STEVIE study that the data cut-off from 16 March 2015 shown in this publication was about 45 months after the start of patient recruitment (June 2011) [16].

The time from the start of the study until the data cut-off is no suitable parameter for assessing the similarity of the studies. A comparison of observation periods is more relevant for the comparability of the studies, particularly as the company did not present event time analyses for the outcomes it included, but relative risks. A comparison of the observation periods on overall survival of the studies BOLT and ERIVANCE revealed a large difference between them. The median observation period in the BOLT study was 21.63 month ([minimum; maximum]: [0.3; 57.8]), and 39.1 months (minimum and maximum not provided) in the ERIVANCE study [13]. The publication on the STEVIE study cited a median follow-up of 17.9 months, for which it was unclear whether this was the overall observation period of overall survival [16]. The company's dossier contained no discussion on the observation periods in the studies included.

Overall, the STEVIE study can be considered equivalent to the ERIVANCE study regarding their relevance for the present benefit assessment. Therefore, the study characteristics of the study and of the interventions are presented together with those for BOLT and ERIVANCE in Appendix A of the full dossier assessment, and the results for patient-relevant outcomes that were recorded in all 3 studies are presented in Appendix B of the full dossier assessment. It was shown that the proportion of events in patient-relevant outcomes of the STEVIE study were closer to those of the BOLT study than those of the ERIVANCE study, which puts the comparison of BOLT and ERIVANCE into perspective.

2.3.3 Assessment of the evidence presented by the company

Comparison of individual study arms

The company's assessment of the added benefit was exclusively based on the comparison of individual arms from different studies. It used the 200 mg arm of the BOLT study and the only arm of the ERIVANCE study for this comparison. Results from comparisons of individual study arms are generally very uncertain, so that conclusions on the added benefit can only be derived in the presence of large effects (see Section 2.7.2.8.1 of the full dossier assessment).

The company presented the following outcomes for the BOLT study: overall survival, progression-free survival, objective response rate, duration of response, time to tumour response, symptoms (recorded with the symptom scales of the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 [EORTC QLQ-C30]), health-related quality of life (recorded with the instruments EORTC QLQ-C30 and Short Form (36) Health Survey [SF-36]) and AEs. The company conducted a comparison with the ERIVANCE study for the outcomes "overall survival", "progression-free survival", "objective response rate", and "AEs". For the comparison of the studies BOLT and ERIVANCE, the

company described statistically significant differences in several outcomes (overall survival, SAEs, muscle spasms, weight loss). The company ignored the results of the STEVIE study on vismodegib, however. In several outcomes, this study showed numerically smaller differences in comparison with the BOLT study than those shown between the studies BOLT and ERIVANCE. As a result, a joint consideration of both vismodegib studies may show no advantage of sonidegib (see Appendix B of the full dossier assessment).

Even under consideration of the studies BOLT and ERIVANCE alone, however, the observed effects were not sufficiently large that they could not be caused by bias alone (see Appendix B of the full dossier assessment). Based on these data, an added benefit of sonidegib in comparison with vismodegib is therefore not proven.

Patient relevance of the outcome "objective response rate"

The company considered the outcome "objective response rate" to be patient relevant. It based this evaluation on the G-BA decision on the benefit assessment of vismodegib [20], among other things. According to this, the outcome "objective response rate" is considered to be patient relevant if an adequate operationalization shows a relevant decrease in tumour size and tumour ulcerations. The company did not present an adequate operationalization, however.

The assessment of the objective response rate in the company's dossier was a composite outcome of several individual components. These components were the following: extent (measured with colour photographs and evaluation of magnetic resonance imaging [MRI] scans, according to Response Evaluation Criteria in Solid Tumours [RECIST] or modified RECIST [mRECIST]), grade of ulceration, and histology of the lesions. These components were integrated in a predefined algorithm for the assessment of the response. The company's dossier did not contain results for these individual components of the outcome.

The operationalization of the outcome "objective response rate" was changed several times in the course of the study. A primary efficacy analysis set (pEAS) was defined, which included all patients with adequate MRI and/or photographic evaluation of their tumours, and which therefore excluded all patients who were not eligible for an evaluation according to mRECIST. This population comprised only about 64% of the randomized laBCC patients.

In its decisions on vismodegib, the G-BA explained that the magnitude and the relevance of tumour response cannot be clearly inferred without knowledge of the individual components of the outcome and information on the extent of the lesions and the grade of ulceration at the start of the study and during the study [20,21]. In the BOLT study however, an objective response could already be determined when there was a 30% reduction in the summarized diameter of the target lesions in the MRI with no photographic evaluation and irrespective of the histological findings. The company's documents contained no information on the extension and the grade of ulceration of individual lesions at the start of treatment and their development during the course of the study, however. This approach used by the company is not comprehensible as these kinds of analyses had already been requested in the benefit assessments

of vismodegib and had been presented in the addendum on the second assessment of vismodegib [3,4,22]. The company only presented aggregate data on the proportion of patients with objective response in its dossier. Hence, the analyses on the outcome "objective response rate" would not be usable even if large effects were present.

2.4 Results

The company presented no suitable data for the assessment of the added benefit of sonidegib in laBCC in its dossier. Consequently, there was no hint of an added benefit of sonidegib in comparison with the ACT. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

No suitable data were available for the assessment of the added benefit of sonidegib in adult patients with laBCC.

Table 5 presents a summary of the probability and extent of the added benefit of sonidegib.

Table 5: Sonidegib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with locally advanced basal cell carcinoma who are not amenable to curative surgery or radiation therapy	**Vismodegib** or best supportive care[b]	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: Best supportive care refers to the therapy that provides the patient with the best possible, individually optimized, supportive treatment to alleviate symptoms and improve the quality of life. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

This assessment deviates from that of the company, which derived a hint of a minor added benefit in its dossier.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no data that would be suitable for the derivation of an added benefit for the benefit assessment.

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Please see full dossier assessment for full reference list.

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