Ivacaftor/tezacaftor/elexacaftor (combination with ivacaftor; cystic fibrosis, 2 to 5 years, F508del mutation, homozygous)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 6 of the dossier assessment *Ivacaftor/Tezacaftor/Elexacaftor (Kombination mit Ivacaftor; zystische Fibrose, 2 bis 5 Jahre, F508del-Mutation, homozygot) – Nutzenbewertung gemäß § 35a SGB V*. 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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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondent and the Mukoviszidose e. V. (Cystic Fibrosis Institute) for participating in the written exchange and for their support. The respondent and the Mukoviszidose e. V. were not involved in the actual preparation of the dossier assessment.

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Ivacaftor, Tezacaftor, Elexacaftor, Cystic fibrosis, Child - Preschool, Benefit Assessment

Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CFTR	cystic fibrosis transmembrane conductance regulator
ELX	elexacaftor
EMA	European Medicines Agency
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IVA	ivacaftor
MF	minimal function
PAES	post-approval efficacy study
PASS	post-authorization safety study
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristic

I 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 ivacaftor/tezacaftor/elexacaftor (in combination with ivacaftor). The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 5 December 2023.

Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as "ivacaftor/tezacaftor/elexacaftor + ivacaftor") in comparison with lumacaftor/ivacaftor as the appropriate comparator therapy (ACT) in cystic fibrosis patients 2 to 5 years of age who are homozygous for the F508del mutation in the cystic fibrosis transmembrane conductance regulator (CFTR) gene.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT**[a]
Patients with cystic fibrosis from 2 to 5 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated lumacaftor/ivacaftor as the ACT, thus following the G-BA's specification.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

The check of completeness of the study pool produced no randomized controlled trials (RCTs) for a direct comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT lumacaftor/ivacaftor in the present therapeutic indication. Due to the lack of studies of direct comparison, the company additionally conducted an information retrieval for non-comparative studies with the intervention and identified the single-arm study VX20-445-111 and its extension study VX20-445-112. For its assessment of the added benefit, the company

primarily used the results of study VX20-445-111. Furthermore, the company sought to transfer study results from older patient groups in the therapeutic indication to the population of children aged 2 to 5 years, which is relevant for the benefit assessment. The company conducted no information retrieval on the ACT, however.

Data presented by the company

Study VX20-445-111 and associated extension study VX20-445-112

Study VX20-445-111 is a single-arm, open-label study investigating treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in cystic fibrosis patients from 2 to 5 years of age. The study included patients who were either homozygous for the F508del mutation in the CFTR gene, or heterozygous for the F508del mutation in the CFTR gene and had a minimal function (MF) mutation on the second allele. In the study, a total of 23 children of the present research question (homozygous for the F508del mutation) were treated with ivacaftor/tezacaftor/elexacaftor granules in combination with ivacaftor granules at a dosage based on body weight and in compliance with the Summary of Product Characteristics (SPC) (Part B of the study). Following the 24-week treatment in Part B of study VX20-445-111, patients had the opportunity to participate in a single-arm extension study (study VX20-445-112), where treatment was continued for a period of up to a further 192 weeks. The primary outcome of Part B of study VX20-445-111 and study VX20-445-112 was the assessment of safety and tolerability based on adverse events as well as laboratory and vital parameters. Further outcomes included pulmonary exacerbations, growth parameters, sweat chloride, lung clearance index$_{2.5}$, and other laboratory parameters.

For its benefit assessment, the company primarily used results from Part B of study VX20-445-111 on the subpopulation of patients who are homozygous for the F508del mutation, and additionally presented results of an interim analysis of study VX20-445-112 after 48 weeks of treatment (corresponding overall to treatment week 72) for the entire study population irrespective of the underlying mutation type.

Company reasoning on transferability

In addition to the results of studies VX20-445-111 and VX20-445-112, the company considered further studies conducted by the company in older age groups in the therapeutic indication, and used these studies for its reasoning in the derivation of the added benefit. To this end, the company referred to previous benefit assessments of ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients of different age groups who are homozygous for the F508del mutation in the CFTR gene (6 to 11 years, 12 years and older), in particular to results of the studies VX18-445-106 (6 to 11 years) and VX18-445-109 (12 years and older), as it assumed that the results were transferable to patients aged 2 to 5 years with the same type of mutation.

Data presented by the company are unsuitable for the benefit assessment

The primary study used by the company to derive added benefit, VX20-445-111, and its extension study VX20-445-112, are each single-arm studies, which do not allow any comparison with the ACT. Hence, these studies are unsuitable for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients aged 2 to 5 years who are homozygous for the F508del mutation.

Due to the lack of studies of direct comparison in children between 2 and 5 years of age, the company's approach of transferring study results from older patients to the population of the present research question is comprehensible. However, the dossier does not include any studies or other information for evaluating the course of disease under the ACT, lumacaftor/ivacaftor, for the population of the present research question. Due to the lack of comparative data, the company's reasoning on transferring added benefit between different age groups is thus based exclusively on the comparison of results on treatment with the intervention.

The company did not provide any information retrieval on non-comparative studies with the ACT, although the company itself had conducted numerous investigations on the treatment of the population of the present research question with lumacaftor/ivacaftor. Although some of the studies conducted by the company itself are cited in Module 3 B of the dossier, the company did not present an evaluation of the available information and results for any of these studies. For the older age groups in the present therapeutic indication, the company also did not present any evaluated data on the relevant studies for the transfer. A comprehensive evaluation of all results on intervention and comparator therapy relevant for the transfer is therefore not available either for the age group of the present research question or for the older age groups.

Irrespective of the described deficiencies, cystic fibrosis is a progressive disease, so that the population of children aged 6 to 11 years should primarily be used for the evaluation and discussion of transferability. For this age group, however, the added benefit was assessed as not proven in the dossier assessment for Commissions A22-16 and A22-22 for the population of children aged 6 to 11 years. It is therefore not possible to transfer the added benefit of older patients to the younger age group, irrespective the inadequate evaluation of the data.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor 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]

Table 3 shows a summary of the probability and extent of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor.

Table 3: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients with cystic fibrosis from 2 to 5 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of this report is to assess the added benefit of ivacaftor/tezacaftor/elexacaftor in combination with ivacaftor (hereinafter referred to as "ivacaftor/tezacaftor/elexacaftor + ivacaftor") in comparison with lumacaftor/ivacaftor as the ACT in cystic fibrosis patients 2 to 5 years of age who are homozygous for the F508del mutation in the CFTR gene.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ivacaftor/tezacaftor/elexacaftor + ivacaftor

Therapeutic indication	**ACT**[a]
Patients with cystic fibrosis from 2 to 5 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee	

The company designated lumacaftor/ivacaftor as the ACT, thus following the G-BA's specification. The company additionally reported that the ACT, lumacaftor/ivacaftor, as well as the drug to be assessed, ivacaftor/tezacaftor/elexacaftor + ivacaftor, were used in addition to individualized therapy to alleviate symptoms and improve the quality of life as in best supportive care. The present benefit assessment was conducted in comparison with lumacaftor/ivacaftor, the ACT specified by the G-BA. Providing additional symptomatic treatment for the patient population is appropriate.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Studies with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

I 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 ivacaftor/tezacaftor/elexacaftor + ivacaftor (status: 15 September 2023)
- bibliographic literature search for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)
- search in trial registries/trial results databases for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)
- search on the G-BA website for ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 5 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on ivacaftor/tezacaftor/elexacaftor + ivacaftor (last search on 18 December 2023); see I Appendix A of the full dossier assessment for the search strategies

Concurring with the company, the check of the completeness of the study pool produced no RCT for the comparison of ivacaftor/tezacaftor/elexacaftor + ivacaftor versus the ACT lumacaftor/ivacaftor in the present therapeutic indication.

Due to the lack of studies of direct comparison, the company additionally conducted an information retrieval for non-comparative studies with the intervention and identified the single-arm study VX20-445-111 [3] and its extension study VX20-445-112 [4]. The company conducted no information retrieval for the ACT. For its assessment of the added benefit, the company primarily used the results of study VX20-445-111. Furthermore, the company sought to transfer study results from older patient groups in the therapeutic indication to the population of children aged 2 to 5 years, which is relevant for the benefit assessment.

The data presented by the company are unsuitable for drawing any conclusions on the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT for the population of the present research question. A detailed rationale is provided below.

Data presented by the company

Study VX20-445-111 and associated extension study VX20-445-112

Study VX20-445-111 is a single-arm, open-label study investigating treatment with ivacaftor/tezacaftor/elexacaftor + ivacaftor in cystic fibrosis patients from 2 to 5 years of age. The study included patients who were either homozygous for the F508del mutation in the

CFTR gene, or heterozygous for the F508del mutation in the CFTR gene and had an MF mutation on the second allele. According to the inclusion criteria, patients had to have a stable disease at the start of treatment.

The study was conducted in 2 parts (Part A and Part B). The duration of treatment was only 15 days in Part A of the study and 24 weeks in Part B. The company only considered Part B for the benefit assessment. In Part B of the study, a total of 23 children of the present research question (homozygous for the F508del mutation) were treated with ivacaftor/tezacaftor/elexacaftor granules in combination with ivacaftor granules at a dosage based on body weight and in compliance with the SPC [5]. Following the 24-week treatment phase, patients had the opportunity to participate in a single-arm extension study (study VX20-445-112), where treatment was continued for a period of up to another 192 weeks. Patients who had reached the age of 6 years during the extension study received the study medication, if possible, in tablet form in a dosage based on body weight in compliance with the SPC [6]. At the time of the benefit assessment, results of Part B of study VX20-445-111 after 24 weeks of treatment and results of an interim analysis of study VX20-445-112 after 48 weeks of treatment (corresponding overall to treatment week 72) were available.

The primary outcome of Part B of study VX20-445-111 and study VX20-445-112 was the assessment of safety and tolerability based on adverse events as well as laboratory and vital parameters. Further outcomes included pulmonary exacerbations, growth parameters, sweat chloride, lung clearance index$_{2.5}$, and other laboratory parameters.

For its benefit assessment, the company primarily used results from Part B of study VX20-445-111 on the subpopulation of patients who were homozygous for the F508del mutation in the CFTR gene, and additionally presented results of the interim analysis of study VX20-445-112 for the entire study population irrespective of the underlying mutation type.

Company reasoning on transferability

In addition to the results of studies VX20-445-111 and VX20-445-112, the company considered further studies conducted by the company in older age groups in the therapeutic indication, and used these studies for its reasoning in the derivation of the added benefit. To this end, the company referred to previous benefit assessments of ivacaftor/tezacaftor/elexacaftor + ivacaftor in patients of different age groups who are homozygous for the F508del mutation in the CFTR gene (6 to 11 years [7], 12 years and older [8]), as it assumed that the results were transferable to patients aged 2 to 5 years with the same type of mutation.

The company reasoned that results were transferable due to a mechanism of action it deemed comparable, the clinical picture of the disease, and sufficiently similar results found in patients from the different age groups. For its reasoning, the company referred to the single-arm VX18-445-106 study [9] and the associated extension study VX19-445-107 [10] for the age

group from 6 to 11 years, and to the RCT VX18-445-109 [11] for the age group 12 years and older. However, the company mentioned results from these studies only in its reasoning for the derivation of added benefit, citing the associated benefit assessment procedures in the respective age groups. The single-arm study VX18-445-106 and the associated extension study VX19-445-107 are described in the dossier assessment for the Commissions A22-16 and A22-22 [12]; the RCT VX18-445-109 was subject of the dossier assessment and the addendum for the Commissions A20-77 and A21-03 [13,14].

Data presented by the company are unsuitable for the benefit assessment

The data presented by the company are unsuitable for assessing the benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT. This is justified below.

Single-arm studies unsuitable for the benefit assessment

The primary study used by the company to derive added benefit, VX20-445-111, and its extension study VX20-445-112, are each single-arm studies, which do not allow any comparison with the ACT. Hence, these studies are unsuitable for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene.

Transfer of results from older patients (6 to 11 years and ≥ 12 years) to the target population unsuitable

The company's approach of transferring study results from older patients to the population of the present research question is plausible in view of the lack of studies of direct comparison in children aged 2 to 5 years. However, the implementation of the company is not suitable for the following reasons.

The company provided no information retrieval for non-comparative studies for the ACT. Thus, the dossier also does not include any studies or other information for evaluating the course of disease under the ACT, lumacaftor/ivacaftor, for the population of the present research question. Due to the lack of comparative data, the company's reasoning on transferring added benefit between different age groups is thus based exclusively on the comparison of results on treatment with the intervention.

However, results on treatment with lumacaftor/ivacaftor from numerous studies conducted by the company itself are available for the patient group of the present research question. In particular, RCT VX16-809-121 [15] should be mentioned here, which was subject of the early benefit assessment procedure for lumacaftor/ivacaftor in patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene [16]. Among others, this study comprises a treatment arm with lumacaftor/ivacaftor in accordance with the ACT specified by

the G-BA for the present benefit assessment (for further information on the study, see dossier assessment on Commission A21-122 [17]). In Module 3 B of the dossier, the company itself referred to this study and also described that numerous data on the use of lumacaftor/ivacaftor in this patient group from everyday health care have become available. In this context, it cited final results of the VX14-809-108 study [18]. This study is a post-authorization safety study (PASS), from which the company had already presented results from an interim analysis on the patient population of the present research question in addition to data from another single-arm study for the early benefit assessment procedure on lumacaftor/ivacaftor. In addition, in Module 4 A of the associated dossier, the company cited the post-authorization efficacy study (PAES) VX18-809-128 on treatment with lumacaftor/ivacaftor, which was still ongoing at the time of the procedure, and which was also referred to by the European Medicines Agency (EMA) in the assessment report on ivacaftor/tezacaftor/elexacaftor for the treatment of the patient group of the present research question with lumacaftor/ivacaftor [19],[20]. It remains unclear whether results from this study have become available in the meantime for the present assessment. Although the studies listed were conducted by the company itself, it did not present an evaluation of the information and results on treatment with the ACT lumacaftor/ivacaftor from these studies for the present benefit assessment.

In principle, a transfer of the study results from older patients to children aged 2 to 5 years would require a complete comparison of all data on the intervention and comparator side to be able to assess whether a transfer is possible. Particularly in view of the numerous studies available to the company on the treatment of the population of the present research question with lumacaftor/ivacaftor, it is not understandable that the company did not conduct any information retrieval on non-comparative studies with the ACT for the benefit assessment and did not present any evaluation of the available data on the comparator therapy.

In addition, the company did not present any evaluated data for the transfer of relevant studies for the older age groups in the present therapeutic indication. In its reasoning, it only cited results in text form from selected studies conducted by the company (the single-arm study VX18-445-106 and the associated extension study VX19-445-107, and the RCT VX18-445-109) for the older age groups. It should also be noted that the comparator therapy (tezacaftor/ivacaftor) used in study VX18-445-109 in patients aged 12 years and older does not correspond to the ACT (lumacaftor/ivacaftor) specified by the G-BA for the research question of patients aged 2 to 5 years with homozygous mutation type to be assessed.

Irrespective of the deficiencies described above, cystic fibrosis is a progressive disease; therefore, the greater the age difference between the population to be analysed and the population from which the transfer is to be made, the more questionable is the transferability of data. For the evaluation and discussion of transferability, the primary population to be used

here should be children aged 6 to 11 years. However, no RCT was available for this age group for the corresponding dossier assessment for Commissions A22-16 and A22-22. Based on the available data, it was not possible to assess the positive and negative effects for this age group (single-arm study on the intervention and incomplete evaluation of supplementary analyses, including the transfer of results from older patients). As part of the corresponding assessment for Commissions A22-16 and A22-22, the added benefit for the population of children aged 6 to 11 years was thus assessed as not proven [12].

For the key outcome in the present therapeutic indication, pulmonary exacerbations, the company itself additionally pointed out in its reasoning that, due to different observation periods and operationalizations of the outcome in the underlying studies, a comparison of the frequency of the occurrence of pulmonary exacerbations between the different age groups is not meaningful.

Summary

The data presented by the company are unsuitable for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. For the primary study used by the company to derive added benefit, VX20-445-111, and its extension study VX20-445-112, this is due to the fact that both of them are single-arm studies, which do not allow any comparison with the ACT. The transfer of study results from older patient groups in the therapeutic indication to the population of children aged 2 to 5 years sought by the company is not suitable for the benefit assessment, in particular because the company did not present any information retrieval on non-comparative studies with the ACT, although the company itself had conducted numerous investigations on the treatment of the population of the present research question with lumacaftor/ivacaftor. The company did not present any evaluation of the available information and results for any of these studies. For the older age groups in the present therapeutic indication, the company also did not present any evaluated data on the relevant studies for the transfer. A comprehensive evaluation of all results on intervention and comparator therapy relevant for the transfer is therefore not available either for the age group of the present research question or for the older age groups. Irrespective of the described deficiencies, cystic fibrosis is a progressive disease, so that the population of children aged 6 to 11 years should primarily be used for the evaluation and discussion of transferability. For this age group, however, the added benefit was assessed as not proven in the dossier assessment for Commissions A22-16 and A22-22 for the population of children aged 6 to 11 years. It is therefore not possible to transfer the added benefit of older patients to the younger age group, irrespective the inadequate evaluation of the data.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT in cystic fibrosis patients aged 2 to 5 years who are homozygous for the F508del mutation in the CFTR gene. There is no hint of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of ivacaftor/tezacaftor/elexacaftor + ivacaftor in comparison with the ACT.

Table 5: Ivacaftor/tezacaftor/elexacaftor + ivacaftor – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with cystic fibrosis from 2 to 5 years of age who are homozygous for the F508del mutation in the CFTR gene	Lumacaftor/ivacaftor	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; CFTR: cystic fibrosis transmembrane conductance regulator; G-BA: Federal Joint Committee		

The assessment described above deviates from the assessment by the company, which derived a hint of considerable added benefit based on the data of the single-arm VX20-445-111 study as well as the transfer of results from patients aged 6 to 11 years, and 12 years and older, to the target population of children aged 2 to 5 years.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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

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