Appendix C Systematic review protocol main (non-transfusions)

Contents

Tables

Abbreviations

CENTRAL	Cochrane Central Register of Controlled Trials
EMBASE	Excerpta Medica dataBASE
MEDLINE	Medical Literature Analysis and Retrieval System Online
PICOS	Population, Interventions, Comparisons, Outcomes, and Study Design
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RBC	Red blood cells
RCT	Randomized controlled trial
SCD	Sickle cell disease
SLR	Systematic literature review
VOC	Vaso-occlusive crisis

1 Introduction

Sickle cell disease (SCD) is a genetic blood disorder characterized by abnormality in the oxygen-carrying protein hemoglobin found in red blood cells (RBCs), depicted by RBCs having a rigid sickle-like shape.[1] Vaso-occlusive crises (VOCs) are the hallmark of SCD, with the disease being associated with serious complications, multi-organ failure, and an increased risk of death.[2] Quality of life is severely impaired for these patients due to recurrent chronic pain crises, regular use of analgesics, repeated hospitalization due to VOCs, and multiple organ failure.[3] The ability to modify the disease and prevent VOC episodes can decrease the risk of complications, organ damage, and the subsequent risk of death in SCD patients, as well as reduce health-resource utilization episodes.

There are limited treatment options are for SCD patients.[2] Hydroxyurea (HU) is the mainstay of treatment; however, majority of patients do not persist on HU, or will not take or cannot take HU, and among the HU-treated patients, some still continue to experience VOCs, fatal organ damage, and a shortened life span.[2] Novartis has developed crizanlizumab for the prevention of VOCs in SCD patients. In a recent randomized, double-blind, placebo-controlled Phase 2 trial, the safety and efficacy of crizanlizumab with or without hydroxyurea was assessed in SCD patients still experiencing ≥2VOCs/ year at time of enrollment.[2] Treatment with high-dose crizanlizumab resulted in a 45.3% reduction in annual rate of VOCs compared to placebo;[2] in addition, the median times to first and second VOC were 2-3 times as long for patients receiving crizanlizumab compared to those receiving placebo.[2]

2 Objective

The key parameters for the economic model relate to the treatment effects of the interventions used for the treatment of SCD. Treatment effects of the relevant alternative interventions of interest will be based on currently available published clinical trial evidence identified by means of a systematic literature review and synthesized with meta-analysis techniques. The current document defines the scope and process of the systematic literature review (SLR).

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3 Methodology

3.1 Eligibility criteria

The SLR will focus on identifying clinical trials evaluating the treatment effects of relevant competing interventions for the treatment of SCD and will be an update of the recent review by Sins et al.[4] The scope will be expanded by incorporating recently published studies and including single arm trials when RCTs are not available for the relevant interventions of interest. Study eligibility criteria are defined in terms of the population, interventions, comparisons, outcomes, and study design (PICOS) outlined in **Table 1**, which will guide the identification and selection of studies considered relevant.

Table 1: Eligibility criteria

Criteria	Description
Population	*Inclusion criteria:* • Adult patients with sickle cell disease
Interventions	• Crizanlizumab • Hydroxyurea • Endari • Voxelotor (GBT440) • Any pharmacological interventions for preventing vaso-occlusive crisis (VOC)*
Comparators	• Placebo or best supportive care • Any of the listed interventions of interest • Any treatment that facilitates an anchored indirect comparison
Outcomes	• Any efficacy related outcome**
Study design	• RCTs • Single-arm trials when RCTs are not available for the interventions of interest
Language	• Only studies published in English

**We exclude interventions such as gene therapy, stem cell therapy and bone marrow transplantation, as these interventions aim to cure sickle cell disease in severe sickle cell disease patients*

***In addition to efficacy outcomes, adverse events are of interest for the review, but will not be used as study selection criteria.*

3.2 Study identification

Relevant studies will be identified by searching the following databases using predefined search strategies: Cochrane Central Register of Controlled Trials (CENTRAL); Medical Literature Analysis and Retrieval System Online (MEDLINE); and Excerpta Medica database (Embase). It should be noted that CENTRAL database does not contain any single-arm (uncontrolled) trials. Therefore, resources for identifying single-arm trials will be MEDLINE and Embase only. This search strategy is based on Sins et al.[4] and constructed

according to the criteria of interest (e.g. outcomes, population, intervention and study design) using MeSH or Emtree terms (thesaurus terms, headings and subheadings) and text words to retrieve potential references. Search strategies have been developed individually for CENTRAL, MEDLINE and Embase and are listed in Appendix A. Please note that the MEDLINE search strategy also aims to identify previously published SLRs and meta-analyses as an additional source to identify relevant primary studies of interest.

Considering the limited searches in Sins et al.[4] due to lack of a clinical trial registry search, a clinical trial registry search on ClinicalTrials.gov will be conducted to identify relevant primary studies of interest, especially unpublished and ongoing studies. This search is based on the search strategy of MEDLINE (**Appendix B**).

Sins et al.[4] completed their literature searches on 30th January 2017. Therefore, all searches on databases will be limited from the date 30th January 2017 onwards, except CENTRAL database. CENTRAL database lacks limit options by date and indexes for identifying date of reference created. Thus, the limit on CENTRAL database will be performed by restricting the publication year from 2017 onwards.

Although it is possible to restrict searches by language (English), it is highly advisable that the search strategy retains high sensitivity (the proportion of references for the desired topic that are retrieved), especially as the estimated number of recalls is small. Therefore, there is no restriction on language at the search stage.

3.3 Study selection

Two reviewers, working independently, will review all abstracts and proceedings identified by the search according to the selection criteria, with the exception of outcome criteria, which will only be applied during the screening of full-text publications. All studies identified as eligible studies during abstract screening will then be screened at a full-text stage by the same two reviewers. Reasons for exclusion will be recorded. The full-text studies identified at this stage will be included for the data extraction. Following reconciliation between the two investigators, a third reviewer will be included to reach consensus on any remaining discrepancies. The process of study identification and selection will be summarized with a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.[5]

3.4 Data extraction

Two reviewers, working independently, will extract data on study characteristics, interventions, patient characteristics, and outcomes for the final list of included studies. Following reconciliation between the two reviewers, a third reviewer will be included to reach consensus on any remaining discrepancies. Data will be stored and managed in a Microsoft Excel workbook.

3.4.1 Study characteristics

The following study characteristics will be extracted:

- Study name
- Study year
- Study authors
- Study design
- Study inclusion criteria
- Study exclusion criteria
- Location of study (countries)
- Year of study initiation and study close
- Follow-up period
- Outcomes
- Patient flow
- Study- and analyses populations (e.g. ITT, mITT, etc.)

3.4.2 Intervention characteristics

The following intervention characteristics will be extracted:

- Treatment regimen
- Treatment dose
- Method of administration
- Frequency of administration
- Duration of treatment
- Concomitant/background therapies
- Compliance/Adherence

3.4.3 Patient characteristics

The following patient characteristics at baseline will be extracted:

- Age
- Gender
- Race and ethnicity
- Other relevant socio-demographics
- Concomitant hydroxycarbamide/hydroxyurea
- Fetal hemoglobin
- Genetic status (HbSS, HbSβo, HbSC, Hbsβ+, other)
- Painful crisis

- Hospital admission frequency
- Painful crisis including home crisis
- Transfusions
- Previous SCD related complications
- Acute chest syndrome
- Avascular osteonecrosis
- Stroke
- Other comorbidities

3.4.4 Outcomes

The following outcomes will be extracted:

- Number of VOCs
- Time to the first VOC
- Duration of VOCs
- % of patients with 0 VOCs/ year
- Number of SCD-related pain days
- Duration of SCD-related pain days
- Number of Hospital Admissions for VOC
- time to first hospital admission for a VOC
- Intensity of pain
- Serious complications
- Organ damage
- Survival
- Quality of life
- Adverse events

For each outcome of interest, the upper & Lower limits of scales along with definition will be reported. For dichotomous outcomes, the number of patients with the event and the number of patients in each treatment arm will be extracted. For continuous outcomes, the change from baseline in all intervention groups will be extracted. If the change from baseline is not provided, the score at end of follow-up and the baseline score will be extracted. For event rates, the number of events, the number of patients in each treatment arm and follow-up or exposure time will be extracted. For time-to-event outcomes, hazard ratios and associated information regarding uncertainty will be extraction. Kaplan Meir curves will be extracted in terms of the proportion of patients who had an event over time using DigitizeIt® in addition to the number of patients at risk over time.

3.4.5 Study quality

Two independent reviewers will assess study quality. Following reconciliation between the two investigators, a third investigator will be included to reach consensus on any remaining discrepancies.

The Cochrane Collaboration's Risk of Bias tool will be used to assess risk of bias in included RCTs (**Appendix C**).[6] This instrument is used to evaluate six key domains: sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias. The risk of bias instrument can be used to assign summary assessments of within-study bias, low risk of bias (low risk of bias for all key domains), unclear risk of bias (unclear risk of bias for one or more key domains), or high risk of bias (high risk of bias for one or more domains).

The Newcastle-Ottawa Scale will be used to assess the quality of single arm studies (**Appendix C**).[7] This instrument is used to evaluate the quality of observational studies based on 1) study group and selection, 2) comparability of the groups within studies, and 3) the ascertainment of either the exposure or outcomes of interest for case-control or cohort studies. Ranking of the study quality will be done by using a 'star system' in which a study can be given a maximum of one star for each numbered item within the "Selection" and "Exposure" categories and a maximum of two stars for "Comparability" category. Two independent reviewers will assess study quality. Following reconciliation between the two investigators, a third investigator will be included to reach consensus on any remaining discrepancies.

4 Discussion

This SLR will involve highly sensitive searches in the peer-reviewed literature as well as searches of recent conferences and clinical trial registrations to identify unpublished completed trials with results available. The review processes will be guided by the pre-defined eligibility criteria established in the review protocol. Data quality will be ensured through the involvement of two independent researchers in the study selection and data extraction phases of the project. The primary outcomes will include median time to the first VOC, median time to the second VOC, median rate of VOCs per year, and overall survival (OS), which reflect the primary outcomes as assessed in the Sins, et al. review as well as many clinical trials for this population. Results of the SLR will help to inform clinicians and decision makers and will provide the foundation to assess the feasibility of performing an NMA.

Despite the strengths of the proposed SLR, some limitations are applicable to all SLRs that should be acknowledged. While there is a clear justification to limit the search and selection to June 20, 2018 based on the scope to update the Sins review, there is always a risk select trials will not be identified that align with the selection criteria. Additionally, as the evidence base is continually growing, any trials published after the search date will not be captured. Further, any trials that are published close to the search date but are not yet indexed in the databases at the time of the search will not be captured by the search of MEDLINE, EMBASE, and Cochrane Central Register of Controlled Trials. Hand searches of other published reviews may help overcome these potential limitations.

As always, the SLR is also limited by the use of published data. There is a risk of publication bias as some clinical trials fail to be published while others are published only in abstract form, which presents limited information. However, an extensive search of conference abstracts will be performed, which may mitigate the impact on the results of the SLR. Posters or slides corresponding to the conference abstracts will be identified where available; however, often conferences do not provide complete information. Moreover, conference results should be interpreted with caution, as they do not undergo the same peer review process as fully published results. Finally, the search and selection will be restricted to trials published in English. Therefore, there is a risk that non-English publications will not be identified.

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Appendix A: Literature search strategies

Table 2: Search strategy for MEDLINE

#	Searches	Concept
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp length of stay/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	anemia, sickle cell/	Population
9	hemoglobin, sickle/	
10	(sickle cell or sickle h?emoglobin or drepanocyt* or drepanotic or drepanocytemia or h?emoglobin-s or Hb-S or sickle an?emia or meniscocytosis).mp.	
11	or/8-10	
12	exp antisickling agents/	Interventions
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	meta analysis.pt.	Systematic review and meta-analysis studies
18	((meta adj analys*) or metaanalys or meta-analys*).ti,ab,sh.	
19	(systematic adj5 (review or overview*)).ti,ab,sh.	
20	or/17-19	
21	16 and 20	
22	clinical trial/	RCTs
23	(clinic adj5 trial*).ti,ab,sh.	

24	single blind method/	
25	double blind method/	
26	random allocation/	
27	placebos/	
28	(placebo or random*).ti,ab,sh.	
29	randomized controlled trial/	
30	(randomized controlled trial or controlled clinical trial or clinical trial).pt.	
31	((single or double or triple or treble) adj (blind or mask*)).ti,ab,sh.	
32	randomi?ed control trial*.tw.	
33	or/22-32	
34	16 and 33	
35	epidemiologic studies/ or case-control studies/ or cross-sectional studies/ or cohort studies/ or follow-up studies/ or longitudinal studies/ or prospective studies/ or retrospective studies/	Single arm trials
36	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 (study or trial* or studies)).ti,ab,kf.	
37	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
38	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab.	
39	Clinical Trial, Phase I.pt.	
40	Clinical Trial, Phase II.pt.	
41	Clinical Trial, Phase III.pt.	
42	(registry or registries).ti,ab,kf,hw.	
43	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kf,hw.	
44	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kf.	
45	(nonrandom* or non-random*).ti,ab,kf.	
46	((control* adj2 before adj2 after) or CBA study).ti,ab,kf.	
47	(all adj3 received).ab.	
48	or/35-47	
49	16 and 48	

50	limit 21 to ed=20170130-20180620	Date limit on rSLR and meta-analysis studies
51	limit 34 to ed=20170130-20180620	Date limit on RCTs
52	limit 49 to ed=20170130-20180620	Date limit on single arm trials

Table 3: Search strategy for EMBASE

#	Searches	
1	exp pain/	Outcomes
2	(pain or painfull).tw.	
3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises).tw.	
4	exp "length of stay"/	
5	(hospital adj3 (admission or stay)).tw.	
6	(patient adj3 (admission or stay)).tw.	
7	or/1-6	
8	sickle cell anemia/	Population
9	hemoglobin S/	
10	(sickle cell or sickle h$emoglobin or drepanocyt* or drepanotic or drepanocytemia or h$emoglobin-s or Hb-S or sickle an$emia or meniscocytosis).mp.	
11	or/8-10	
12	antisickling agent/	Intervention
13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440).mp.	
14	(8 or 9 or 10) and prevent vaso-occlusiv*.tw.	
15	or/12-14	
16	7 and 11 and 15	
17	randomized controlled trial/	RCTs

18	(RCT or randomi#ed or randomi#ation).ab,ti,kw,hw.	
19	(random* adj3 (administ* or allocat* or assign* or class* or control* or determine* or divide* or distribut* or expose* or fashion* or number* or place* or recruit* or subsitut* or treat*)).ab,kw.	
20	trial.ti.	
21	crossover procedure/	
22	((singl* or doubl* or tripl* or trebl*) adj3 (blind* or mask* or dumm*)).ti,ab,kw,hw.	
23	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 4 clinical trial/	
24	or/17-23	
25	16 and 24	
26	prospective study/ or retrospective study/ or longitudinal study/ or cohort analysis/ or cross-sectional study/ or case control study/ or population based case control study/	Single-arm trials
27	((epidemiologic or prospective or retrospective or cross-sectional or feasibil* or pilot or case control* or cohort or longitudinal) adj3 study).ti,ab,kw.	
28	(case control* or cross-sectional or cohort? or follow-up or followup or longitudinal or prospective or retrospective or observational or population).ti.	
29	((cohort? adj2 (analys* or compar* or data or study or studies)) or (population adj2 (based or data* or study or studies or register? or registry or registries or survey? or surveillance))).ab,kw.	
30	(registry or registries).ti,ab,kw,hw.	
31	(nonrandom* or non-random*).ti,ab,kw.	
32	((control* adj2 before adj2 after) or CBA study).ti,ab,kw.	
33	((single adj arm*) or single-arm or single group or uncontrol* or un-control* or "no control*").ti,ab,kw.	
34	(all adj3 received).ab.	
35	phase 2 clinical trial/ or phase 3 clinical trial/ or phase 1 clinical trial/	
36	((phase 1 or Phase i or Phase 2 or Phase ii or Phase 3 or Phase iii) and (trial* or study or studies)).ti,ab,kw.	
37	or/26-36	
38	16 and 37	
39	limit 25 to em=201705-201825	Date limit on RCTs
49	limit 38 to em=201705-201825	Date limit on single arm trials

Table 4: Search strategy for Cochrane Register of Controlled Trials

#	Searches	
#1	MeSH descriptor: [Pain] explode all trees	Outcomes
#2	(pain or painfull):ti,ab,kw	
#3	(venoocclusive or "vein occlusive" or "vein interruption" or "vein obstruction" or "vein occlusion" or "vena obstruction" or "veno occlusive" or "venous obstruction" or "venous occlusion" or vaso-occlusiv* or crisis or crises):ti,ab,kw	
#4	MeSH descriptor: [Length of Stay] explode all trees	
#5	(hospital near/3 (admission or stay)):ti,ab,kw	
#6	(patient near/3 (admission or stay)):ti,ab,kw	
#7	#1 or #2 or #3 or #4 or #5 or #6	
#8	MeSH descriptor: [Anemia, Sickle Cell] this term only	Population
#9	MeSH descriptor: [Hemoglobin, Sickle] this term only	
#10	(sickle cell or sickle h*emoglobin or drepanocyt* or drepanotic or drepanocytemia or h*emoglobin-s or Hb-S or sickle an*emia or meniscocytosis):ti,ab,kw	
#11	#8 or #9 or #10	
#12	MeSH descriptor: [Antisickling Agents] explode all trees	Interventions
#13	(antisickling agent* or sickling inhibitor* or Efaproxiral or Dimethyl Adipimidate or desickling agent* or cetiedil or glutamine or hydroxyurea or rivipansel or senicapoc or tucaresol or velaresol or crizanlizumab or endari or voxelotor or GBT440):ti,ab,kw	
#14	(#8 or #9 or #10) and prevent vaso-occlusiv*	
#15	#11 or #12 or #13	
#16	#7 and #11 and #14	

Appendix B: ClinicalTrials.gov search

Table 6: Search strategy for ClinicalTrials.gov*

#	Searches	Search column
#1	Anemia, Sickle Cell OR Sickle Beta Thalassemia OR Sickle Cell Anemia OR Sickle Cell trait	Condition or disease
#2	SCD OR SCA OR Sickle	Other terms
#3	Drug OR Placebo OR Crizanlizumab OR Hydroxyurea OR Endari OR Voxelotor OR GBT440 OR hydroxycarbamide	Intervention/treatment
#4	pain OR hospitalisation OR hospitalization OR (hospital AND (admission OR stay)) OR crisis OR VOC OR ((vaso OR vein OR vena OR venous) AND (occlusive OR occlusive OR interruption OR obstruction)) OR survival OR quality of life	Outcome Measures
	#1 or #2 or #3 or #4	

*Advanced Search option without any restrictions except search strings listed.

Appendix C: Risk of bias and quality assessment

Table 5: Cochrane risk of bias assessment tool[6]

Domain	Support for judgment	Review authors' judgment
Selection bias		
Random sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.	Selection bias (biased allocation to interventions) due to inadequate generation of a randomized sequence.
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment.	Selection bias (biased allocation to interventions) due to inadequate concealment of allocations prior to assignment.
Performance bias		
Blinding of participants and personnel *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Performance bias due to the knowledge of the allocated interventions by participants and personnel during the study.
Detection bias		
Blinding of outcome assessment *Assessments should be made for each main outcome (or class of outcomes)*	Describe all measures used, if any, to blind outcome assessors from knowledge of which intervention a participant received. Provide any information relating to whether the intended blinding was effective.	Detection bias due to the knowledge of the allocated interventions by outcome assessors.
Attrition bias		
Incomplete outcome data *Assessments should be made for each main outcome (or class of outcomes)*	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis. State whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any re-inclusions in analyses performed by the review authors.	Attrition bias due to amount, nature or handling of incomplete outcome data.
Reporting bias		
Selective reporting	State how the possibility of selective outcome reporting was examined by the review authors, and what was found.	Reporting bias due to selective outcome reporting.
Other bias		
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool. If particular questions/entries were pre-specified in the review's protocol, responses should be provided for each question/entry.	Bias due to problems not covered elsewhere in the table.

Table 6: Newcastle-Ottawa quality assessment scale – cohort studies[7]

Domain	Response
Selection	
1. Representativeness of the exposed cohort	a. Truly representative of the average _____ (describe) in the community* b. Somewhat representative of the average _____ in the community* c. Selected group of users (e.g. nurses, volunteers) d. No description of the derivation of the cohort
2. Selection of the non-exposed cohort	a. Drawn from the same community as the exposed cohort* b. Drawn from a different source c. No description of the derivation of the non-exposed cohort
3. Ascertainment of exposure	a. Secure record (e.g. surgical records)* b. Structured interview* c. Written self-report d. No description
4. Demonstration that outcome of interest was not present at start of study	a. Yes* b. No
Comparability	
1. Comparability of cohorts on the basis of the design or analysis	a. Study controls for _____ (select the most important factor)* b. Study controls for any additional factor (this criteria could be modified to indicate specific control for a second important factor)*
Outcomes	
1. Assessment of outcome	a. Independent blind assessment* b. Record linkage* c. Self-report d. No description
2. Was follow-up long enough for outcomes to occur	a. Yes (select an adequate follow up period for outcome of interest)* b. No
3. Adequacy of follow up of cohorts	a. Complete follow up - all subjects accounted for* b. Subjects lost to follow up unlikely to introduce bias - small number lost - > % (select an adequate %) follow up, or description provided of those lost)* c. Follow up rate < % (select an adequate %) and no description of those lost d. No statement

Note: A study can be awarded a maximum of one star for each numbered item within the selection and outcomes categories. A maximum of two stars can be given for comparability.

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