EPAR Search for the CONFIRMS Non-Proportional Hazards Research Project

Tobias Fellinger, Florian Klinglmüller

AGES

Overall Project

AGES

- Review of „Statistical methods for time-to-event endpoints with non-proportional hazards in clinical trials pivotal for benefit risk decision making"
- Project consisted of multiple parts:
  - Literature review
  - **EPAR review**
  - Simulation study
  - Case studies
- Results from EPAR were the basis for:
  - Parametric simulations (choice of scenarios, parameters, analysis methods)
  - Non-parametric simulations (sampling from digitized Kaplan-Meier Curves)
  - Choice of case studies

Objective of the EPAR Review

Objective: Identify EMA marketing authorization procedures where nonproportional hazards (NPH) were of concern in the efficacy assessment in order to:

- **identify scenarios** and parameter ranges for a simulation study to evaluate method performance across a range of relevant settings,
- derive **case studies** to illustrate findings based on actual trials,
- derive **regulatory recommendations** for future practice.

A protocol (JBI Scoping Review Template, PRISMA-ScR) was developed and registered[1] before study initiation

[1]https://catalogues.ema.europa.eu/node/3500/administrative-details

Search and Screening

- paediatricdata.eu was searched to identify paragraphs in EPARs matching a predefined list of keywords
- Identified paragraphs were screened by pairs of independent reviewers to exclude procedures clearly not related to NPH issues
- For selected procedures full-text EPARs were reviewed by pairs of independent reviewers to check eligibility criteria and extract relevant information for the review
- Duplicate procedures were removed, disagreements on inclusion were resolved by a third reviewer
- 92 procedures were found, for 29 the full-text was screened and 16 were finally included in the review

Data Extraction

- Use of a standardised extraction form with pre-specified items
- Instructions for Extraction included
  - Use of the extraction form, fields, links, …
  - Structure of the EPAR documents
  - Data to be extracted, including how the data will be used later
- Data extraction forms for included procedures were merged and copy-edited
- Additional data were extracted from extraction forms or EPARs (e.g. digitized the KM curves using the R package *IPDfromKM*, HR, time of separation) – in one case from corresponding scientific publication

EPARs as Research Tool

Pros:

- Studies / Cases are by definition relevant to regulatory science
  - Methods that are actually used in MAAs
  - Includes information on the assessment of the regulators
  - Relevant populations, realistic parameter values
- Easily accessible and searchable
- Well structured (as compared to publications in academic journals)

Cons:

- Selection bias: withdrawn MAAs are not included
- Reporting and level of detail is heterogeneous
- Initial assessment before final decision on MAA is not included
  - Intially submitted methodology that was not agreed to by the regulators might not be reported in the EPAR
- No info on methodology & guidance under development

Austrian Agency for Health
and Food Safety

Tobias Fellinger, Florian Klinglmüller

Austrian Medicines & Medical Devices Agency

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Inclusion and Exclusion of Search Results

- 133 paragraphs from 92 procedures were identified in the database search
- 28 out of 92 procedures were included by at least one reviewer following paragraph screening
- 1 procedure (negative opinion) was referred to us by EMA
- 29 procedures were included for full-text review
- 16 procedures were included following full-text review
- 2 procedures reported results on 2 main studies
- **In total data from 18 trials was extracted**

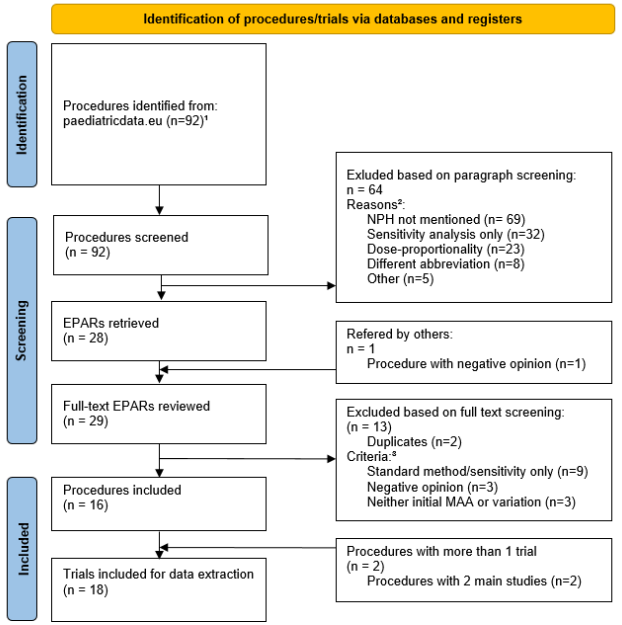


Figure 1. PRISMA 2020 flow diagram – identified and included procedures for the regulatory procedure review.
[1]Total number of paragraphs returned in search (n=133)
[2]Numbers include duplicate mentions per procedure across paragraphs and reviewers (i.e. overall n=266)
[3]Numbers include duplicate mentions per procedure across eligibility criteria and reviewers

EPAR Review - PRISM Flowchart

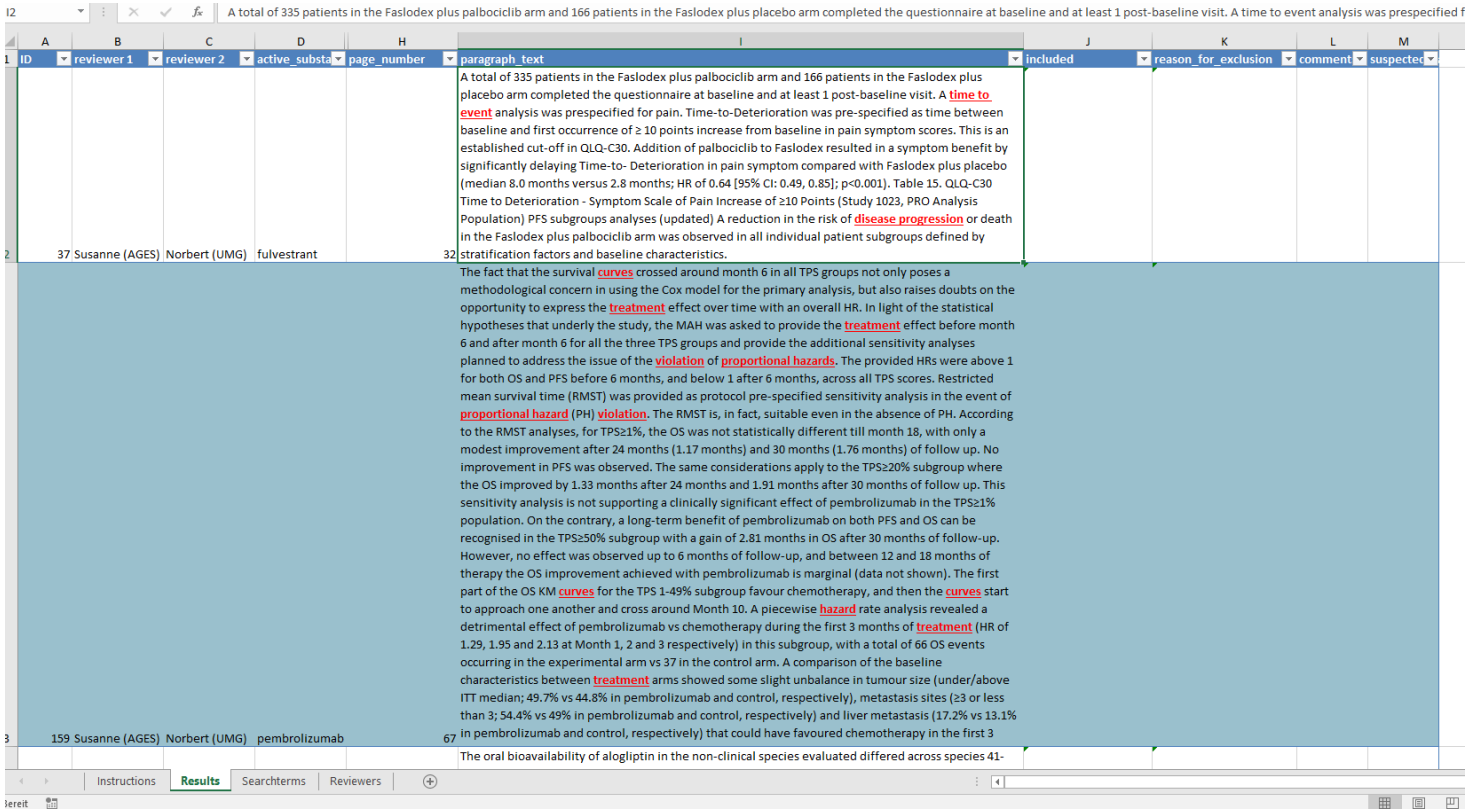
Simulation Parameters Derived from EPAR Review

- Sample size
- Length of recruitment
- Length of followup
- Median survival time in both study arms
- Frequency of censoring / loss to followup
- For different scenarios
  - Time of separation of survival curves
  - Time of crossing of survival curves
  - Freqency of intercurrent event of treatment switching

#	Search Terms	Identified Procedures
1	"non-proportional hazard" OR "non-proportional hazards" OR "nonproportional hazard" OR "nonproportional hazards" OR "nonproportional hazard" OR "nonproportional hazards"	10
2	"non-proportionality" OR "nonproportionality" OR "non proportionality"	5
3	("NPH" OR "NPHs" OR "non PH" OR "non PHs" OR "non-PH" OR "non-PHs") AND ("assumption" OR "assumptions")	3
4	"proportional hazard" OR "proportional hazards" OR "hazard assumption" OR "hazard assumptions"	246
5	"violation" OR "violations" OR "violated" OR "violat*"	481
6	#4 AND #5	14
7	#1 OR #2 OR #3 OR #6	40
8	"delayed treatment effect" OR "delayed treatment effects"	4
9	#7 OR #8	41
10	crossing AND (hazard OR hazards)	22
11	crossing AND (curve OR curves)	69
12	"delayed effect" OR "delayed effects"	60
13	delayed AND treatment	1906
14	"treatment switch*" OR "heterogeneous patient*" OR "heterogeneous population*" OR "disease progression*"	7463
15	#10 OR #11 OR #12 OR #13 OR #14	9404
16	"hazard assumption" OR "hazard assumptions" OR time-to-event OR "time to event"	1326
17	#15 AND #16	47
18		
19	wie 17	
20	#9 OR #19	133

Search terms with detailed results

Search Terms and Results

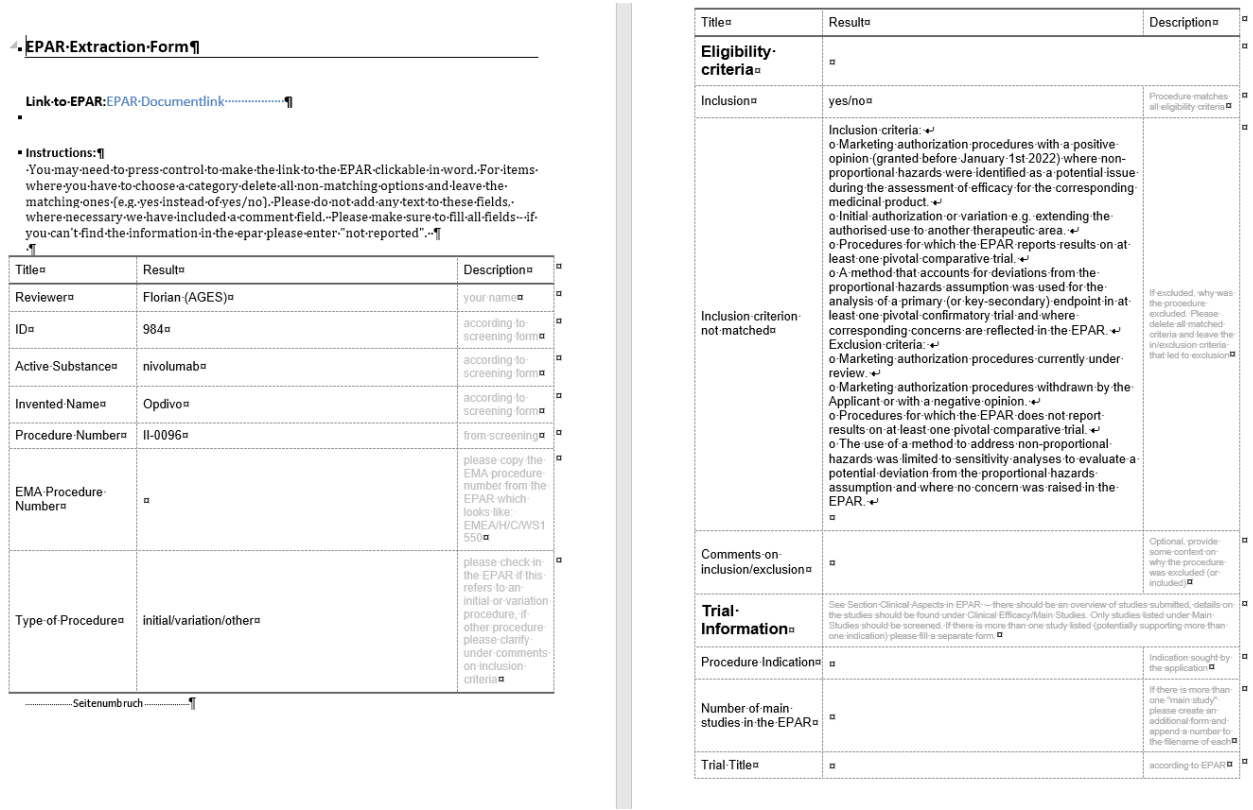


	A	B	C	D	H	I	J	K	L	M
1	ID	reviewer 1	reviewer 2	active_substa	page_number	paragraph_text	included	reason_for_exclusion	comment	suspected
2	37	Susanne (AGES)	Norbert (UMG)	fulvestrant	32	A total of 335 patients in the Faslodex plus palbociclib arm and 166 patients in the Faslodex plus placebo arm completed the questionnaire at baseline and at least 1 post-baseline visit. A time to event analysis was prespecified for pain. Time-to-Deterioration was pre-specified as time between baseline and first occurrence of ≥ 10 points increase from baseline in pain symptom scores. This is an established cut-off in QLQ-C30. Addition of palbociclib to Faslodex resulted in a symptom benefit by significantly delaying Time-to- Deterioration in pain symptom compared with Faslodex plus placebo (median 8.0 months versus 2.8 months; HR of 0.64 [95% CI: 0.49, 0.85]; p<0.001). Table 15. QLQ-C30 Time to Deterioration - Symptom Scale of Pain Increase of ≥10 Points (Study 1023, PRO Analysis Population) PFS subgroups analyses (updated) A reduction in the risk of disease progression or death in the Faslodex plus palbociclib arm was observed in all individual patient subgroups defined by stratification factors and baseline characteristics.				
3	159	Susanne (AGES)	Norbert (UMG)	pembrolizumab	67	The fact that the survival curves crossed around month 6 in all TPS groups not only poses a methodological concern in using the Cox model for the primary analysis, but also raises doubts on the opportunity to express the treatment effect over time with an overall HR. In light of the statistical hypotheses that underly the study, the MAH was asked to provide the treatment effect before month 6 and after month 6 for all the three TPS groups and provide the additional sensitivity analyses planned to address the issue of the violation of proportional hazards. The provided HRs were above 1 for both OS and PFS before 6 months, and below 1 after 6 months, across all TPS scores. Restricted mean survival time (RMST) was provided as protocol pre-specified sensitivity analysis in the event of proportional hazard (PH) violation. The RMST is, in fact, suitable even in the absence of PH. According to the RMST analyses, for TPS≥1%, the OS was not statistically different till month 18, with only a modest improvement after 24 months (1.17 months) and 30 months (1.76 months) of follow up. No improvement in PFS was observed. The same considerations apply to the TPS≥20% subgroup where the OS improved by 1.33 months after 24 months and 1.91 months after 30 months of follow up. This sensitivity analysis is not supporting a clinically significant effect of pembrolizumab in the TPS≥1% population. On the contrary, a long-term benefit of pembrolizumab on both PFS and OS can be recognised in the TPS≥50% subgroup with a gain of 2.81 months in OS after 30 months of follow-up. However, no effect was observed up to 6 months of follow-up, and between 12 and 18 months of therapy the OS improvement achieved with pembrolizumab is marginal (data not shown). The first part of the OS KM curves for the TPS 1-49% subgroup favour chemotherapy, and then the curves start to approach one another and cross around Month 10. A piecewise hazard rate analysis revealed a detrimental effect of pembrolizumab vs chemotherapy during the first 3 months of treatment (HR of 1.29, 1.95 and 2.13 at Month 1, 2 and 3 respectively) in this subgroup, with a total of 66 OS events occurring in the experimental arm vs 37 in the control arm. A comparison of the baseline characteristics between treatment arms showed some slight unbalance in tumour size (under/above ITT median; 49.7% vs 44.8% in pembrolizumab and control, respectively), metastasis sites (≥3 or less than 3; 54.4% vs 49% in pembrolizumab and control, respectively) and liver metastasis (17.2% vs 13.1% in pembrolizumab and control, respectively) that could have favoured chemotherapy in the first 3				
4						The oral bioavailability of alogliptin in the non-clinical species evaluated differed across species 41-				

Instructions | Results | Searchterms | Reviewers

Screenshot of Screening Form

Screening Form



EPAR·Extraction·Form¶

Link·to·EPAR: EPAR·Documentlink¶

Instructions:¶
·You·may·need·to·press·control·to·make·the·link·to·the·EPAR·clickable·in·word.·For·items·where·you·have·to·choose·a·category·delete·all·non·matching·options·and·leave·the·matching·ones·(e.g.·yes·instead·of·yes/no).·Please·do·not·add·any·text·to·these·fields,·where·necessary·we·have·included·a·comment·field.·Please·make·sure·to·fill·all·fields·–·if·you·can't·find·the·information·in·the·epar·please·enter·"not·reported".·¶
·¶

Title¤	Result¤	Description¤
Reviewer¤	Florian·(AGES)¤	your·name¤
ID¤	984¤	according·to·screening·form¤
Active·Substance¤	nivolumab¤	according·to·screening·form¤
Invented·Name¤	Opdivo¤	according·to·screening·form¤
Procedure·Number¤	II-0096¤	from·screening¤
EMA·Procedure·Number¤	¤	please·copy·the·EMA·procedure·number·from·the·EPAR·which·looks·like:·EMEA/H/C/WS1550¤
Type·of·Procedure¤	initial/variation/other¤	please·check·in·the·EPAR·if·this·refers·to·an·initial·or·variation·procedure,·if·other·procedure·please·clarify·under·comments·on·inclusion·criteria¤

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Title¤	Result¤	Description¤
Eligibility·criteria¤	¤	
Inclusion¤	yes/no¤	Procedure·matches·all·eligibility·criteria¤
Inclusion·criterion·not·matched¤	Inclusion·criteria:·↵ o·Marketing·authorization·procedures·with·a·positive·opinion·(granted·before·January·1st·2022)·where·non-proportional·hazards·were·identified·as·a·potential·issue·during·the·assessment·of·efficacy·for·the·corresponding·medicinal·product.·↵ o·Initial·authorization·or·variation·e.g.·extending·the·authorised·use·to·another·therapeutic·area.·↵ o·Procedures·for·which·the·EPAR·reports·results·on·at·least·one·pivotal·comparative·trial.·↵ o·A·method·that·accounts·for·deviations·from·the·proportional·hazards·assumption·was·used·for·the·analysis·of·a·primary·(or·key-secondary)·endpoint·in·at·least·one·pivotal·confirmatory·trial·and·where·corresponding·concerns·are·reflected·in·the·EPAR.·↵ Exclusion·criteria:·↵ o·Marketing·authorization·procedures·currently·under·review.·↵ o·Marketing·authorization·procedures·withdrawn·by·the·Applicant·or·with·a·negative·opinion.·↵ o·Procedures·for·which·the·EPAR·does·not·report·results·on·at·least·one·pivotal·comparative·trial.·↵ o·The·use·of·a·method·to·address·non-proportional·hazards·was·limited·to·sensitivity·analyses·to·evaluate·a·potential·deviation·from·the·proportional·hazards·assumption·and·where·no·concern·was·raised·in·the·EPAR.·↵ ¤	If·excluded,·why·was·the·procedure·excluded.·Please·delete·all·matched·criteria·and·leave·the·in/exclusion·criteria·that·led·to·exclusion¤
Comments·on·inclusion/exclusion¤	¤	Optional,·provide·some·context·on·why·the·procedure·was·excluded·(or·included)¤
Trial·Information¤	See·Section·Clinical·Aspects·in·EPAR·–·there·should·be·an·overview·of·studies·submitted,·details·on·the·studies·should·be·found·under·Clinical·Efficacy/Main·Studies.·Only·studies·listed·under·Main·Studies·should·be·screened.·If·there·is·more·than·one·study·listed·(potentially·supporting·more·than·one·indication)·please·fill·a·separate·form.¤	
Procedure·Indication¤	¤	Indication·sought·by·the·application¤
Number·of·main·studies·in·the·EPAR¤	¤	If·there·is·more·than·one·"main·study"·please·create·an·additional·form·and·append·a·number·to·the·filename·of·each¤
Trial·Title¤	¤	according·to·EPAR¤

Example Extraction Form

Extraction Form