Precision medicine in regulatory decision making

Bakker, Elisabeth; Starokozhko, Viktoriia; Kraaijvanger, Jet W M; Heerspink, Hiddo J L; Mol, Peter G M

Published in:
Clinical and translational science

DOI:
10.1111/cts.13641

Received: 22 July 2023 | Revised: 22 July 2023 | Accepted: 21 August 2023

DOI: 10.1111/cts.13641

ARTICLE

Precision medicine in regulatory decision making: Biomarkers used for patient selection in European Public Assessment Reports from 2018 to 2020

Elisabeth Bakker[1] | **Viktoriia Starokozhko**[1,2] | **Jet W. M. Kraaijvanger**[2,3] | **Hiddo J. L. Heerspink**[1] | **Peter G. M. Mol**[1,2]

[1]University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[2]Dutch Medicines Evaluation Board, CBG-MEB, Utrecht, The Netherlands

[3]VU University Amsterdam, Amsterdam, The Netherlands

Correspondence
Peter G. M. Mol, Department of Clinical Pharmacy & Pharmacology, University Medical Center Groningen, Internal postcode AP50, Hanzeplein 1, PO Box 30.001, Groningen 9700 RB, The Netherlands.
Email: p.g.m.mol@umcg.nl

Funding information
Innovative Medicines Initiative, Grant/Award Number: 115974; Horizon Europe Research and Innovation Actions, Grant/Award Number: 101095146

Abstract

Biomarkers can guide precision medicine in clinical trials and practice. They can increase clinical trials' efficiency through selection of study populations more likely to benefit from treatment, thus increasing statistical power and reducing sample size requirements or study duration. We performed a narrative synthesis to explore biomarker utilization for patient selection to guide precision medicine trials in marketing authorization dossiers of centrally approved medicines in Europe between 2018 and 2020 and analyzed in-depth those that eventually included biomarkers in the medicines' indications. From 119 eligible products, 26 included a biomarker in the indication, of which most were oncology products ($n = 15$). Included biomarkers were often known from literature or from previously approved products in the European Union or the United States. Additionally, 52 dossiers mentioned one or more biomarkers for patient selection in their clinical efficacy and safety information. Although these were not always included in the medicines' indication, they were often implicitly embedded in condition definitions adopted from clinical guidelines or practice. In 15 out of the 26 medicines with a biomarker-guided indication, only biomarker-positive populations were included in the main clinical studies supporting the marketing authorization. These studies were mostly randomized controlled trials or single-arm trials; only two products were studied for multiple indications in an innovative basket trial. Definitions of biomarkers could be subject of debate and needed adaptation after post hoc analyses requested by the assessment committee in four cases, stressing the importance of thorough justification of these definitions to include the right population for an optimal benefit–risk balance, enabling precise medicine.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

To our knowledge, only few studies on biomarker utilization in recently approved medicines have been performed, mostly of quantitative nature or for a specific disease area.

WHAT QUESTION DID THIS STUDY ADDRESS?

How often are biomarkers used for patient selection and how are they applied in clinical trials to guide precision medicine in marketing authorization documents of recent centrally approved medicines in Europe?

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study provides an in-depth review of the inclusion of biomarkers in the clinical development programs of centrally approved medicines in Europe, describing their use in defining study populations, study designs, and medicines' indications and how they were assessed by regulators.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

Biomarkers are crucial for the advancement of precision medicine. The results give insights in the role of biomarkers to guide development of precision medicines and in the regulatory evaluation of such medicines. The results may be of use for future precision medicines' and biomarkers' development, stimulating broader implementation of precision medicine.

INTRODUCTION

Precision, or personalized medicine, tailors prevention or treatment strategies for patients, addressing the challenges of common medicines not being effective in large numbers of patients and rising healthcare costs.[1] With the introduction of precision medicine and the increasing use of biomarkers, clinical trials needed a shift toward a more patient-centered approach.[2] Biomarkers, defined by the Biomarkers, EndpointS, and other Tools (BEST) resource as "a defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or biological responses to an exposure or intervention, including therapeutic interventions,[3]" can guide precision medicine in clinical trials and may increase their efficiency by selecting the right population in which the treatment effect is maximized and sample size and/or study duration can be reduced. As a result, biomarkers may advance the development of new medicines.[4] They can be used to identify patients with a given condition or disease state (diagnostic biomarkers) or predict an individual's disease progression and increased risk of experiencing a certain clinical event (prognostic biomarkers). Additionally, they can predict an individual's response to a therapeutic agent and thereby identify patients that are more likely to benefit from a given treatment or identify patients that are likely to be harmed by it (predictive biomarkers).[3]

The two most common applications of these biomarkers are for stratification and enrichment of trials. In case of stratification, biomarkers are measured in all patients and used to balance the treatment arms based on the biomarker status or levels. In an enrichment approach, the study population is enriched by selecting a subset of patients that are more likely to show benefit of the treatment based on certain biomarker criteria. In both applications, biomarker-negative populations may still be included to justify the biomarker use for patient selection, unless earlier studies or strong mechanistic rationale have determined absence of a response in the biomarker-negative population. In cases where there is uncertainty about the cutoff values of the biomarker and/or the responsiveness of biomarker-negative patients, inclusion of a reasonable sample of the biomarker-negative population becomes especially relevant.[5,6] Biomarker-driven strategies can be applied in traditional randomized controlled trials (RCTs), but also in single-arm trials (SATs) and innovative trial designs, such as basket or umbrella trials, where multiple indications and multiple candidate medicines can be tested within one trial.[7]

Before new biomarkers are accepted by regulators, they need to be thoroughly validated.[8] Regulators like the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) provide guidance to applicants regarding the use of biomarkers in multiple ways. Thus, several

procedures are put in place in which applicants' biomarker validation plans intended for clinical medicines development could be discussed, such as the Innovation Task Force briefing meetings and the Qualification of Novel Methodologies procedures at the EMA, and the Biomarker Qualification Program at the FDA.[9–11] A positive outcome in the last two procedures assures the validity of and qualifies the biomarker for a specific context of use. According to previous studies, only a few biomarkers have been qualified by regulatory agencies up to now.[12] A number of these biomarkers are shown to be used in clinical studies after qualification in the qualified context of use or in an alternative context of use.[13] However, these qualified biomarkers reflect only a proportion of biomarkers used in the context of recently authorized medicines.[14] For example, biomarkers used and accepted in the evidence generation for recently authorized medicines may have been validated within the clinical development program that supported a marketing authorization application, or already in an earlier stage.[13,15] With this study, we aimed to explore biomarker utilization and their application in clinical trials to guide precision medicine in marketing authorization documents of recent centrally approved medicines in Europe.

METHODS

We performed a narrative synthesis of marketing authorization dossiers of medicinal products that were authorized from January 1. 2018, until December 31, 2020, that used biomarkers for patient selection.

Study population

European Public Assessment Reports (EPARs) of all European central marketing authorization procedures are publicly available on the EMA website. For this study, EPARs of medicines for human use as assessed by the Committee for Medicinal Products (CHMP) for human use that were approved from January, 2018 to December 31, 2020, were selected for screening from the table of all EPARs for human and veterinary medicines (accessed on the EMA website on January 28, 2021: https://www.ema.europa.eu/en/medicines/download-medicine-data - european-public-assessment-reports-(epar)-section).[16] EPARs of generic medicines, biosimilars, hybrid medicinal products (Article 10.3), well-established use applications (Article 10a), fixed dose combination applications (Article 10b), informed consent applications (Article 10c), and known active substance applications according to Directive 2001/83/EC[17] were excluded, because relevant information on the used biomarkers is likely to be presented only in the EPARs of original medicines.

Review process and data extraction

For the included EPARs, hereafter referred to as "dossiers," data on the medicines' characteristics (active substance and therapeutic areas), regulatory characteristics (type of approval and orphan status), and characteristics of the biomarkers (type of biomarker and type of use) were extracted from the abovementioned downloaded EPAR table. Additionally, section 4.1 "indication" and subsections "mechanism of action" and "clinical efficacy and safety" (sometimes also called "clinical efficacy" or "clinical trial efficacy") of section 5.1 "pharmacodynamic properties" of the Summary of Product Characteristics (SmPC) were extracted.[18] The extracted data were screened by two researchers independently (authors E.B. and V.S.) for including biomarkers in the indication (section 4.1) or mentioning biomarkers as inclusion criteria in the clinical studies in the clinical efficacy and safety information (section 5.1) of the SmPC. For this purpose, the previously mentioned definition for biomarkers of the BEST resource was used.[3] Product dossiers for which biomarkers were identified in one or both sections were included in the analysis. Biomarkers used to identify vulnerable populations that are usually excluded from clinical trials (e.g., pregnancy, elderly, and hepatic/renal impairment) were not included in the analysis, because we expect those to be present for nearly all of the studies.[19] The biomarkers were categorized by two researchers independently (authors E.B. and V.S.) according to the BEST resource on the type of use of biomarkers (i.e., diagnostic, prognostic, and predictive)[3] as well as the composition of biomarkers (i.e., soluble, imaging, functional [i.e., biophysical], genetic, clinical score, and histology). In case of discrepancies between the results, these were discussed with a third researcher (author P.G.M.M.) until consensus was reached. One dossier could comprise multiple biomarkers and one biomarker could have been assigned to multiple type of use categories.

From product dossiers for which a biomarker was mentioned in the indication, additional data on the medicines' clinical studies were extracted by two researchers (authors E.B. and J.W.M.K.). Specifically, for the studies presented as the main clinical studies in the dossiers, information was collected on the study design, whether only biomarker-positive populations were included in the studies or both biomarker-positive and -negative populations, and how the use of a biomarker was taken into account in the analysis of the study results. In this paper, biomarker-positive will be defined as "meeting the given biomarker criteria," which can be, for example, presence or absence of a certain mutation, but also a range of values. This means that biomarker-positive may also mean sometimes that the values are below a certain threshold

(e.g., <50 RNA copies/mL) if this was the given biomarker definition.

For product dossiers that mentioned biomarkers for patient selection in the clinical efficacy and safety information of the SmPC, but did not include those biomarkers in the indication, keyword searches were performed for "indication" and the specific biomarker(s) terms. Data on the indication proposed by the applicant and the approved indication as well as comments with regard to the indication were extracted by two researchers (authors E.B. and V.S.).

Data analysis

Descriptive statistics were used to summarize the extracted information from the dossiers. Chi-squared tests were performed between product subgroups for which biomarkers used for patient selection were included in sections 4.1 and 5.1 to analyze the differences in the type of approval (conditional/exceptional or standard), orphan indication status (yes or no), and the most frequent (i.e., ≥5 products) pharmacotherapeutic subgroups (based on level 2 Anatomical Therapeutic Class[20]). The additionally extracted data included in the in-depth analyses were analyzed descriptively, and illustrative examples were presented.

RESULTS

Dossier selection

In total, 247 medicines were approved in the European Union by the EMA between January 1, 2018, and December 31, 2020 (Figure 1). After excluding generics ($n=41$) and biosimilars ($n=31$), 175 dossiers were screened to select the complete dossiers of original medicines. From the 119 eligible dossiers, section 4.1 ("indication") and section 5.1 ("mechanism of action" and "clinical efficacy and safety") of the SmPCs were screened for inclusion of biomarkers. Of those 119 dossiers, 52 mentioned 86 biomarkers for patient selection in the clinical efficacy and safety information of the SmPC. In 26 dossiers, 33 biomarkers were included in the medicine's therapeutic indication. The dossiers were not necessarily overlapping; in three cases, the biomarkers were included in the indication, but were not specified as inclusion criteria for the clinical studies presented in the clinical efficacy and safety information.

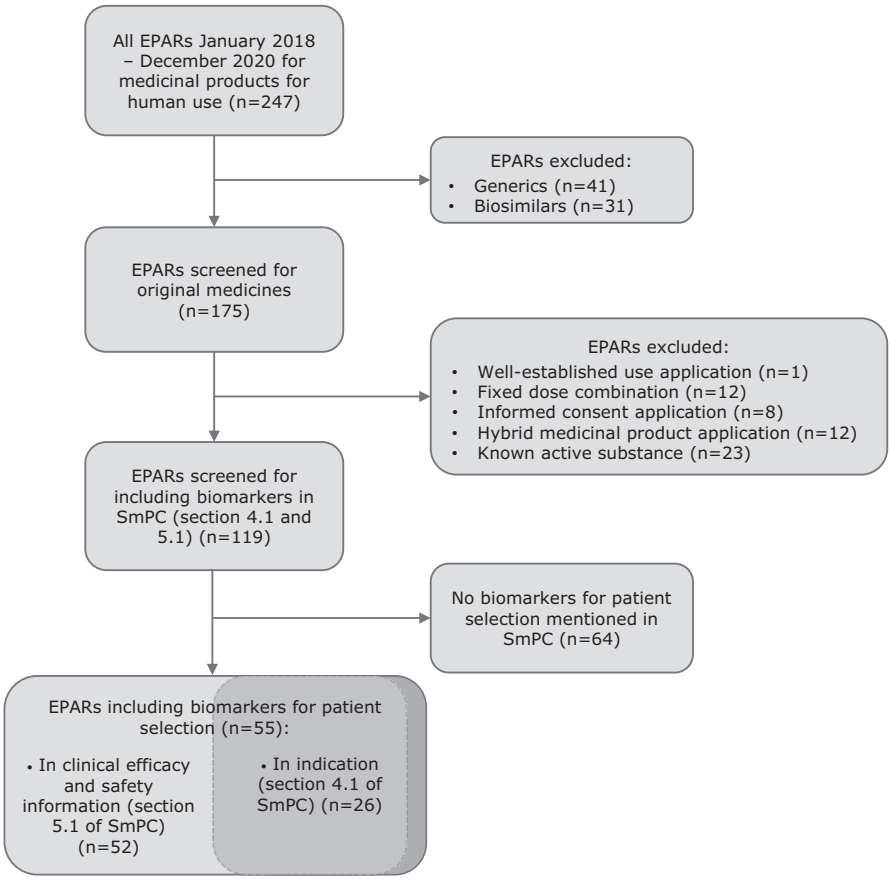

FIGURE 1 Selection procedure of product dossiers of original medicines approved from January 2018 to December 2020 by the European Medicines Agency that include biomarkers. EPARs, European public assessment reports; SmPC, summary of product characteristics.

Regulatory and medicine characteristics

Dossiers that did and did not present biomarkers used for patient selection in the indication and/or clinical efficacy and safety information were similar with regard to their regulatory characteristics (i.e., type of approval and orphan status; Table 1). However, some differences were shown regarding pharmacotherapeutic subgroups. Dossiers with biomarkers in the indication showed a higher proportion of antineoplastic agents, both compared to all 119 approved dossiers in our study period and compared to the dossiers that did include a biomarker for patient selection in the clinical efficacy and safety information, but not in the indication. None of the antibacterials for systemic use and vaccines included a biomarker for patient selection in the indication or the clinical efficacy and safety information.

Biomarker characteristics

The 86 different biomarkers for patient selection mentioned in the clinical efficacy and safety information (section 5.1) included 25 soluble biomarkers (e.g., fasting insulin), 21 genetic biomarkers (e.g., genetic mutations), 11 functional biomarkers (e.g., respiratory rate), 15 clinical scores (e.g., psoriasis area and severity index), 10 histology biomarkers (e.g., percentage of superficial cells in vaginal smear), and four imaging biomarkers (e.g., multiple sclerosis lesions; Figure 2). The biomarkers were used for diagnostic ($n=75$), prognostic ($n=31$), and/or predictive ($n=25$) purposes, which were largely overlapping.

Of the 33 biomarkers included in the 26 medicines' therapeutic indication (section 4.1), the majority were predictive ($n=27$), and mostly genetic ($n=15$) and histology ($n=8$) biomarkers (Figure 2).

Biomarker-driven clinical studies

In 11 out of 26 medicines that did include a biomarker in the indication, the general population (i.e., both biomarker-positive and biomarker-negative populations), were included in the main clinical study or studies (Table 2). In one of these (alpelisib), the population was divided in a biomarker-positive and a biomarker-negative cohort, after which they were randomized. In three cases, stratification was randomized by biomarker status (cabotegravir, pegvaliase, and sotagliflozin). In seven cases (avapritinib, betibeglogene autotemcel, crisaborole, durvalumab, gemtuzumab ozogamicin, lorlatinib, and neratinib) subgroup analyses based on the biomarker status (i.e., different biomarker ranges, genetic mutations, or presence/absence of a biomarker) were performed. In 15 out of 26 medicines, only the biomarker-positive population was included in the analysis of the main clinical studies. In 10 cases (abemaciclib, autologous CD34+ cells encoding arylsulfatase A [*ARSA*] gene, binimetinib, encorafenib, entrectinib, gilteritini, imlifidase, ivacaftor/tezacaftor/elexacaftor, luspatercept, onasemnogene abeparvovec, and voretigene neparvovec), the population included in the indication was in line with the population included in the main clinical studies. In the other four cases (brigatinib, larotrectinib, rucaparib, and talazoparib), subgroup analyses were performed based on different biomarker statuses to determine the most suitable target population to be included in the indication.

For the majority ($n=16$) of products, the main clinical studies included one or more RCTs. In eight dossiers, singe-arm designs were used as main clinical studies (autologous CD34+ cells encoding *ARSA* gene, avapritinib, betibeglogene autotemcel, brigatinib, imlifidase, lorlatinib, onasemnogene abeparvovec, and rucaparib), of which five predictive genetic or histological biomarkers were used to select the patient population. In two dossiers (i.e., entrectinib and larotrectinib), a basket study design was applied as (part of) the main clinical studies.

Biomarker establishment and threshold determination

Of the 26 medicines that included biomarkers in their indication, for two of them, the biomarker inclusion was not initially proposed by the applicant but was requested by the CHMP following evaluation (durvalumab and gemtuzumab ozogamicin). For four, the threshold of the biomarkers as used in the clinical studies had to be redefined for the final indication in agreement with CHMP recommendations (cabotegravir, crisaborole, durvalumab, and sotagliflozin). For example, in the case of durvalumab, expression of the programmed cell death ligand-1 (PD-L1) by greater than or equal to 1% cells needed to be included in the indication, because durvalumab selectively blocks PD-L1 binding. This threshold was based on the retrospective analysis of progression free survival in less than 1% versus greater than or equal to 1% PD-L1 expression, requested by the CHMP.[21] Similarly, in case of gemtuzumab ozogamicin for de novo CD33-positive acute myeloid leukemia "CD33-positive" was added to the indication considering the product's mechanism of action, which is CD33-directed.[22] In the indication of cabotegravir, the included biomarker was eventually defined according to the standard criteria for virological failure.[23] For

TABLE 1 Regulatory characteristics and medicine characteristics.

		BM in 4.1			BM in 5.1					
	Total	Yes	No	*p* value	Yes	No	*p* value	BM in 5.1 but not 4.1	BM in 5.1 and 4.1	*p* value
Number of products	119	26	93		52	67		29	23	
Type of approval										
Standard	93	20	73	0.131	39	54	0.505	22	17	0.762
Conditional approval	16	6	10		9	7		3	6	
Exceptional approval	6	0	6		2	4		2	0	
Accelerated approval	5	1	4	0.919	3	2	0.453	2	1	0.406
Orphan indication	37	11	26	0.162	17	20	0.740	7	10	0.352
Pharmacotherapeutic subgroup				0.006**			0.021*			0.003**
Drugs used in diabetes (A10)	5	1	4	0.919	2	3	0.865	2	0	0.406
Other alimentary tract and metabolism products (A16)	6	1	5	0.753	2	4	0.599	2	0	0.600
Antihemorrhagics (B02)	8	0	8	0.122	2	6	0.270	2	0	0.966
Antibacterials for systemic use (J01)	6	0	6	0.184	0	6	0.027*	0	0	0.154
Antivirals for systemic use (J05)	10	1	9	0.343	4	6	0.805	3	1	0.665
Vaccines (J07)	9	0	9	0.099	0	9	0.006**	0	0	0.077
Antineoplastic agents (L01)	25	15	10	0.000**	14	11	0.163	0	14	0.001**
Immunosuppressants (L04)	10	1	9	0.343	6	4	0.277	5	1	0.049*
Other	18	4	14	0.967	10	8	0.271	6	4	0.336

Abbreviation: BM, biomarker.

*$p < 0.05$. **$p < 0.01$.

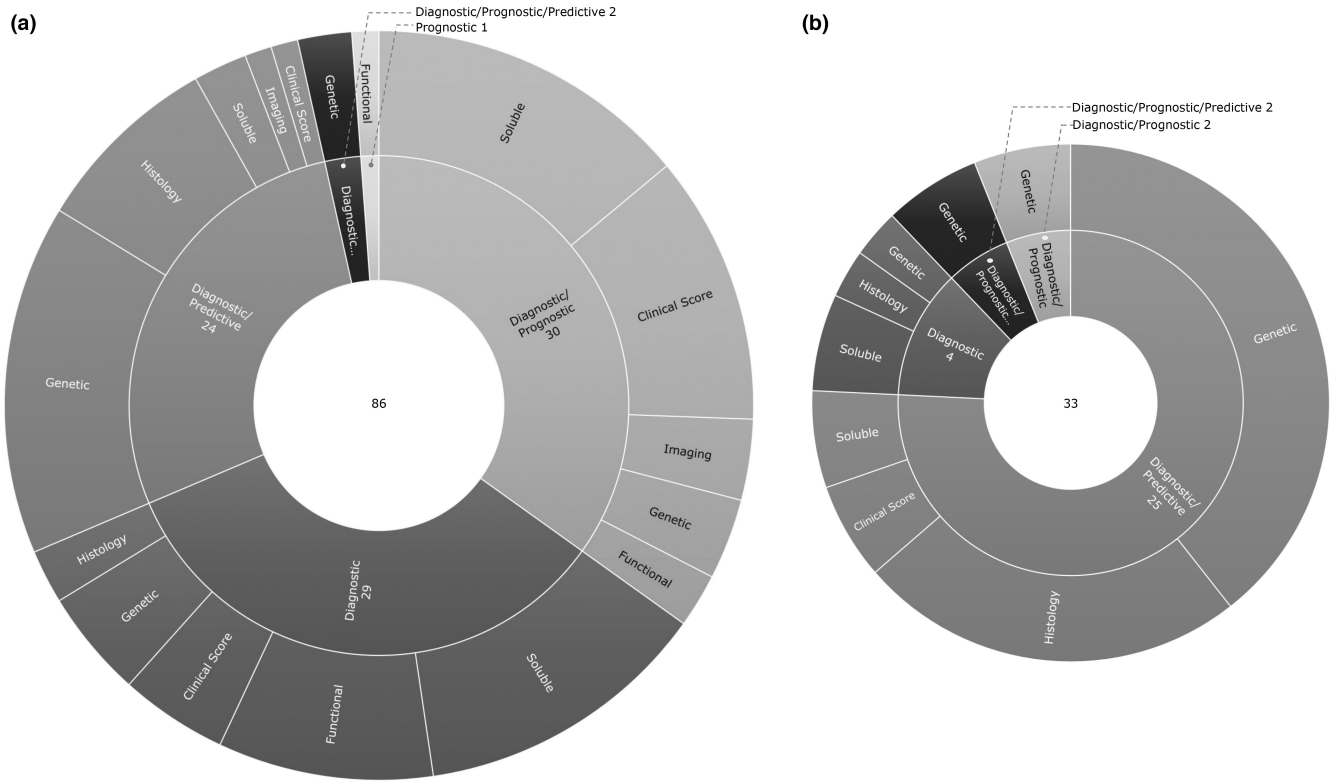

FIGURE 2 Biomarkers for patient selection in medicines' clinical efficacy and safety information (a) and indications (b) presented by type of use (i.e., diagnostic, prognostic and/or predictive) and by biomarker types (e.g., soluble, imaging, functional, genetic, clinical score, or histology).

crisaborole for atopic dermatitis, subgroup analyses were performed for different biomarker ranges upon request of the CHMP (i.e., percentage of body surface area [BSA] 0.1–<16%, 16–40%, and >40%), which indicated a higher rate of adverse events with higher doses and higher percentage of BSA affected. Additionally, the number of patients included with the percentage of BSA greater than 40 was overall low, and the restriction of the indication to patients with percentage of BSA less than or equal to 40% was, therefore, considered a valid solution to circumvent the uncertainties on clinical effects in patients with percentage of BSA greater than 40.[24] For the main clinical studies investigating sotagliflozin for diabetes type 1, the randomization was stratified by body mass index (BMI) at screening in groups less than 25 kg/m^2 and greater than or equal to 25 kg/m^2. In the pooled analysis, a subgroup analysis was performed for BMI less than 27 kg/m^2 and greater than or equal to 27 kg/m^2. Although efficacy was shown for all subgroups, the CHMP considered the benefit–risk balance only to be positive for the BMI greater than or equal to 27 kg/m^2 subgroup for several reason, including that patients with higher BMI receive higher insulin doses, which had shown to result in a decreased risk of the adverse effect being diabetic ketoacidosis. Additionally, this subgroup had an unmet medical need, and the weight reduction and the reduction of systolic blood pressure were considered of greatest importance in overweight patients.[25]

In some dossiers, the included biomarkers were not discussed further, and the proposed indications were based on the trial patient selection. For instance, presence of anaplastic lymphoma kinase (ALK) gene re-arrangements was included as a predictive biomarker for brigatinib and lorlatinib, because anti-ALK activity of the products was established in cell lines in the nonclinical studies.[26,27] Similar cases included binimetinib and encorafenib.[28,29] However, in eight cases where only the biomarker-positive population was included in the main clinical studies, it was proposed by either CHMP or the applicant to further explore the used biomarker and/or other biomarkers post-approval (abemaciclib, autologous CD34+ cells encoding *ARSA* gene, binimetinib, encorafenib, imlifidase, ivacaftor/tezacaftor/elexacaftor, onasemnogene abeparvovec, and rucaparib).

Biomarkers not included in the indication

In 29 cases, one or more biomarkers used for patient selection were mentioned in clinical efficacy and safety information but were not included in the medicine's indication

TABLE 2 Overview of medicines that included a biomarker in the indication.

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Alpelisib	• Hormone receptor (HR) • Human epidermal growth factor receptor 2 (HER2) • PIK3CA mutation	For the treatment of postmenopausal women, and men with *HR-positive, HER2-negative*, advanced breast cancer with a *PIK3CA* mutation in combination with fulvestrant after disease progression following an endocrine-based regimen	RCT	• Postmenopausal women and men with HR-positive, HER2-negative advanced breast cancer whose disease progressed on or after aromatase inhibitor treatment	Assigned to 2 cohorts PIK3CA+, PIK3CA−, thereafter randomized
Cabotegravir	HIV-1 RNA copies	In combination with rilpivirine injection, for the treatment of HIV-1 infection in adults who are virologically suppressed (HIV-1 RNA < 50 copies/mL) on a stable antiretroviral regimen without present or past evidence of viral resistance to, and no prior virological failure with agents of the non-nucleoside reverse transcriptase inhibitor and integrase inhibitor class	Pooled analysis of 3 RCTs	• HIV-1 infected, antiretroviral treatment-naive men or women aged ≥18 years, with HIV-1 RNA ≥1000 c/mL • HIV-1 infected men or women aged ≥18 years, on uninterrupted current regimen (either the initial or second antiretroviral regimen) for at least 6 months prior to screening, with HIV-1 RNA <50 c/mL in the 12 months prior to screening • HIV-1 infected antiretroviral treatment-experienced adult subjects who are virologically suppressed (HIV-RNA < 50 c/mL) on a stable antiretroviral regimen	Randomization 1:1 stratified by HIV-1 RNA < 100,000 c/mL, HIV-1 RNA ≥ 100,000 c/mL
Pegvaliase	Blood phenylalanine	For the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 μmol/L) despite prior management with available treatment options	RCT	• Patients with PKU 18 to 70 years of age	Randomization stratified by mean blood phenylalanine levels ≤600 μmol/L, >600 μmol/L

(Continues)

TABLE 2 (Continued)

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Sotagliflozin	BMI	As an adjunct to insulin therapy to improve glycemic control in adults with T1DM with a BMI ≥ 27 kg/m^2, who have failed to achieve adequate glycemic control despite optimal insulin therapy	Pooled analysis of 3 (ongoing) RCTs	• Patients 18 years and older with a diagnosis of T1DM made at least 1 year prior to informed consent, a Screening A1C of 7.0% to 11.0% (inclusive), an estimated glomerular filtration rate (eGFR) > 45 mL/min/1.73 m^2, and a triglyceride value • Patients 18 years and older with a diagnosis of T1DM made at least 1 year prior to informed consent, a Screening A1C of 7.0% to 11.0% (inclusive), an eGFR >45 mL/min/1.73 m^2, and a triglyceride value • Patients ≥18 years of age, with a BMI ≥18.5 kg/m^2, a confirmed diagnosis of T1DM made at least 1 year before screening, and a screening A1C of 7.0% to 11.0%, (inclusive), an eGFR >45 mL/min/1.73 m^2, and a triglyceride value	Randomization stratified by BMI at screening (<25 kg/m^2, ≥25 kg/m^2), also analyzed for <27 kg/m^2 and ≥ 27 kg/m^2
Avapritinib	Platelet-derived growth factor receptor alpha (PDGFRA) D842V mutation	As monotherapy for the treatment of adult patients with unresectable or metastatic GIST harboring the *PDGFRA D842V* mutation	SAT	Patients with unresectable GIST: • that had progressed following imatinib and at least 1 of the following: sunitinib, regorafenib, sorafenib, dasatinib, pazopanib or an experimental kinase inhibitor agent, and did not have a D842V mutation in PDGFRA; or • that had a D842V mutation in PDGFRA; or • that had progressed and/or had experienced intolerance to imatinib and not have received additional kinase inhibitor therapy, and did not have a known D842V mutation in PDGFRA	Subgroup analysis no D842V mutation, D842V mutation

TABLE 2 (Continued)

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Betibeglogene autotemcel	β0/β0 genotype	Treatment of patients 12 years and older with TDT who do not have a β0/β0 genotype, for whom HSC transplantation is appropriate but a human leukocyte antigen (HLA)-matched related HSC donor is not available	Pooled analysis of 4 SATs	• Patients with TDT who do not have a β0 mutation at both alleles of the β-globin gene (i.e., non-β0/β0) • Patients with TCT and non-β0/β0 genotype • Patients with β0/β0 genotype and non-β0/β0 genotype • Patients with TDT with β0/β0, IVS-I-110/ β0, and IVS-I-110/IVS-I-110 genotypes	Subgroup analysis non-β0/β0, β0/β0 genotype
Crisaborole	BSA	For treatment of mild to moderate atopic dermatitis in adults and pediatric patients from 2 years of age with ≤40% BSA affected	2 RCTs	• Children and adults 2 years of age and older with atopic dermatitis affecting at least 5% of the BSA (excluding the scalp) at baseline/ day 1, and a score of mild (2) or moderate (3) on a 5-grade ISGA that rated erythema, induration/ papulation, and oozing/crusting	Subgroup analysis per % BSA (0.1%–<16%, 16–≤40 and >40% BSA)
Durvalumab	PD-L1 expression	As monotherapy is indicated for the treatment of locally advanced, unresectable NSCLC in adults whose tumors express *PD-L1* on ≥1% of tumor cells and whose disease has not progressed following platinum-based chemoradiation therapy	RCT	• Patients with locally advanced, unresectable NSCLC (stage III) who have not progressed following definitive, platinum-based, concurrent chemoradiation therapy. The PACIFIC study enrolled patients regardless of their PD-L1 expression	Subgroup analysis PD-L1 < 25%, ≥25% Retrospective analysis PD-L1 < 1%, ≥1%
Gemtuzumab ozogamicin	CD33 antigen	For combination therapy with daunorubicin and cytarabine for the treatment of patients age 15 years and above with previously untreated, de novo CD33-positive AML, except APL	RCT	• Patients with AML aged 50–70 years	Subgroup analysis CD-33 expression <30%, ≥30%, <70%, ≥70%
Lorlatinib	ALK	As monotherapy is indicated for the treatment of adult patients with ALK-positive advanced NSCLC whose disease has progressed after: alectinib or ceritinib as the first ALK TKI therapy; or crizotinib and at least one other ALK TKI	SAT	• Patients with histologically or cytologically confirmed metastatic NSCLC that carried an ALK re-arrangement	Subgroup analysis ALK+ and ALK−

(Continues)

TABLE 2 (Continued)

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Neratinib	• HR • HER2	For the extended HR-positive, HER2-overexpressed/amplified breast cancer and who are <1 year from the completion of prior adjuvant trastuzumab-based therapy	RCT	• Women with early stage HER2 overexpressed (HER2+) breast cancer. Primary tumor ER/ PR status had to be known before study entry. Patients were ER and/or PR-positive (HR+) or ER and PR–negative (HR−).	Subgroup analysis HER2+/ HR+, HER2+/HR−,
Brigatinib	ALK	As monotherapy for the treatment of adult patients with ALK-positive advanced NSCLC previously treated with crizotinib	SAT (2 regimens)	• Patients with ALK+ locally advanced or metastatic NSCLC whose disease has progressed on therapy with crizotinib	Only BM+ population, subgroup analysis primary, secondary ALK+
Larotrectinib	*NTRK* gene fusion	As monotherapy is indicated for the treatment of adult and pediatric patients with solid tumors that display a *NTRK* gene fusion, who have no satisfactory treatment options	Pooled analysis of basket study and 2 dose-escalation studies	• Patients aged 12 years and older with recurrent advanced solid tumors with an NTRK1, NTRK2, or NTRK3 gene fusion • NTRK fusion patients contributing to, as well as non-NTRK fusion patients • Pediatric patients with advanced solid or primary central nervous system tumors; NTRK fusion patients, as well as non-NTRK fusion patients	Only BM+ population in pooled analysis, subgroup analysis per NTRK fusion type
Rucaparib	BRCA gene mutation	As monotherapy treatment of adult patients with platinum sensitive, relapsed or progressive, *BRCA*-mutated (germline and/or somatic), high-grade epithelial ovarian, fallopian tube, or primary peritoneal cancer, who have been treated with two or more prior lines of platinum-based chemotherapy, and who are unable to tolerate further platinum-based chemotherapy	Pooled analysis of two SATs	• Patients with relapsed, platinum-sensitive disease who received 2 to 4 prior treatment regimens and were known to harbor a gBRCA mutation based on results from local testing • Patients with relapsed high-grade serous or endometrioid epithelial ovarian, fallopian tube, or primary peritoneal cancer	Only BM+ population in pooled analysis, subgroup analysis for gBRCA, sBRCA, BRCA1 and BRCA2 gene mutations, BRCA+ versus BRCA− in safety analysis

TABLE 2 (Continued)

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Talazoparib	• BRCA gene mutation • HER2	As monotherapy for the treatment of adult patients with germline *BRCA1/2*-mutations, who have *HER-2* negative locally advanced or metastatic breast cancer. Patients should have previously been treated with an anthracycline and a taxane in the (neo)adjuvant, locally advanced or metastatic setting unless patients were not suitable for these treatments	RCT	• BRCA mutation subjects with locally advanced and/or metastatic breast cancer, who have received prior chemotherapy regimens for metastatic disease	Only BM+ population, subgroup analysis per BRCA status (1 vs. 2)
Abemaciclib	• HR • HER2	For the treatment of women with *HR-positive, HER2-negative* locally advanced or metastatic breast cancer in combination with an aromatase inhibitor or fulvestrant as initial endocrine-based therapy, or in women who have received prior endocrine therapy	2 RCTs	• Women with hormone receptor positive, HER2 negative locally advanced or metastatic breast cancer • Postmenopausal women with hormone receptor-positive, HER2-negative locoregionally recurrent or metastatic breast cancer with no prior systemic therapy in this disease setting	Only BM+ population
Autologous CD34+ cells encoding *ARSA* gene	*ARSA* gene mutation	For the treatment of MLD characterized by biallelic mutations in the *ARSA* gene leading to a reduction of the ARSA enzymatic activity: • in children with late infantile or early juvenile forms, without clinical manifestations of the disease, • in children with the early juvenile form, with early clinical manifestations of the disease, who still have the ability to walk independently and before the onset of cognitive decline	SAT with external comparator	• 22 MLD subjects, 9 late infantile MLD, and 13 early juvenile MLD confirmed by *ARSA* enzymatic activity and genetic analysis	Only BM+ population
Binimetinib	BRAF V600 mutation	In combination with encorafenib for the treatment of adult patients with unresectable or metastatic melanoma, with *BRAF V600* mutation	RCT	• Patients with unresectable or metastatic BRAF V600 mutant melanoma	Only BM+ population

(Continues)

TABLE 2 (Continued)

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Encorafenib	BRAF V600 mutation	In combination with binimetinib is indicated for the treatment of adult patients with unresectable or metastatic melanoma with a *BRAF V600* mutation	RCT	Patients with unresectable or metastatic BRAF V600 mutant melanoma	Only BM+ population

Entrectinib	• NTRK gene fusion
	• ROS proto-oncogene 1, receptor tyrosine kinase (ROS1)
		• As monotherapy for the treatment of adult and pediatric patients 12 years of age and older, with solid tumors that have a *NTRK* gene fusion, who have a disease that is locally advanced, metastatic or where surgical resection is likely to result in severe morbidity, and
		  • who have not received a prior NTRK inhibitor
		  • who have no satisfactory treatment options.p.25
		• As monotherapy is indicated for the treatment of adult patients with *ROS1-positive*, advanced non-small cell lung cancer (NSCLC) not previously treated with ROS1 inhibitors
			Basket-trial	Patients with metastatic solid tumor that harbors an NTRK1/2/3, ROS1, or ALK gene rearrangement	Only BM+ population

Gilteritinib	Fms Related Receptor Tyrosine Kinase 3 (FLT3)	As monotherapy for the treatment of adult patients who have relapsed or refractory AML with a *FLT3 mutation*	RCT (vs. salvage chemotherapy)	Patients with relapsed refractory AML with FLT3 mutation	Only BM+ population, sensitivity analysis for subgroups ITD and TKD mutations
Imlifidase	Positive crossmatch	For desensitization treatment of highly sensitized adult kidney transplant patients with positive crossmatch against an available deceased donor. The use should be reserved for patients unlikely to be transplanted under the available kidney allocation system including prioritization programs for highly sensitized patients	SAT	Patients on the kidney transplant waitlist with a living or deceased donor with a positive crossmatch test	Only BM+ population

TABLE 2 (Continued)

Medicine	Biomarker	Indication	Main study/ studies design(s)	Population included in main studies	BM-guided analysis in main studies
Ivacaftor, tezacaftor, elexacaftor	F508del mutation in the cystic fibrosis transmembrane conductance regulator (*CFTR*) gene	For the treatment of CF in patients aged 12 years and older who are homozygous for the F508del mutation in the *CFTR* gene (F/F) or heterozygous for F508del in the *CFTR* gene with a F/MF	2 RCTs with open-label extension	• Subjects with CF who are heterozygous for the F508del mutation and a F/MF • Subjects with CF who are homozygous for the F508del mutation (F/F)	Only BM+ population
Luspatercept	Ring sideroblasts	For the treatment of adult patients with transfusion-dependent anemia due to very low, low and intermediate-risk MDS with ring sideroblasts, who had an unsatisfactory response to or are ineligible for erythropoietin-based therapy. For the treatment of adult patients with transfusion-dependent anemia associated with beta thalassemia.	2 RCTs (one for each indication)	Subjects with very low, low, or intermediate risk (according to International Prognostic Scoring System – Revised), ring sideroblast positive MDS who required red blood cell transfusions for anemia and are refractory to (nonresponse or response that is no longer maintained), intolerant of, or ineligible for (serum erythropoietin >200 U/L) erythropoiesis-stimulating agent treatment	Only BM+ population
Onasemnogene abeparvovec	• Mutation in survival of motor neuron 1 (SMN1) gene • SMN2 gene copies	For the treatment of: • patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and a clinical diagnosis of SMA type 1, or • patients with 5q SMA with a bi-allelic mutation in the *SMN1* gene and up to 3 copies of the *SMN2* gene	SAT with external comparator	Patients with SMA type 1 who were either symptomatic or pre-symptomatic with no functional *SMN1* gene and 1 or 2 copies of *SMN2* and who are <6 months (<180 days) of age at the time of gene replacement therapy	Only BM+ population
Voretigene neparvovec	RPE65 mutations	For the treatment of adult and pediatric patients with vision loss due to inherited retinal dystrophy caused by confirmed biallelic *RPE65* mutations and who have sufficient viable retinal cells	2 RCTs	• Patients ≥3 years old with confirmed RPE65 mutations • Patients with Leber congenital amaurosis due to RPE65 mutations	Only BM+ population

Abbreviations: ALK, anaplastic lymphoma kinase; AML, acute myeloid leukemia; APL, acute promyelocytic leukemia; BM+, biomarker-positive; BMI, body mass index; BSA, body surface area; CF, cystic fibrosis; F/MF, minimal function mutation; GIST, gastrointestinal stromal tumor; HSC, hematopoietic stem cell; ISGA, investigator static global assessment; MDS, myelodysplastic syndrome; MLD, metachromatic leukodystrophy; NSCLC, non-small cell lung cancer; RCT, randomized controlled trial; SAT, single-arm trial; SMA, spinal muscular atrophy; T1DM, type 1 diabetes mellitus; TDT, transfusion-dependent β-thalassemia; TKI, tyrosine kinase inhibitor.

(Table 1). An in-depth analysis of the corresponding dossiers did show that even though the biomarkers were not specified in the medicine's indication, they were often embedded in wording and definitions of diseases or disease states adopted from clinical guidelines or practices. For example, in case of tildrakizumab, which is indicated "for treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy," "moderate to severe" being defined by baseline scores of BSA involvement greater than or equal to 10%, Psoriasis Area Severity Index score greater than or equal to 12, and Physician Global Assessment of at least moderate disease (≥3). The dossier stated "This is in line with the CHMP guideline on clinical investigation of medicinal products indicated for the treatment of psoriasis (CHMP/EWP/2454/02 corr)."[30] Another example is ropeginterferon alfa-2b that is indicated "as monotherapy in adults for the treatment of polycythemia vera without symptomatic splenomegaly," where the World Health Organization includes the JAK2V617F or JAK2 exon 12 genetic mutation as mandatory part of diagnosis of polycythemia vera, as was stated in the dossier.[31]

One example where biomarker was deliberately not included in the indication was benralizumab for eosinophilic asthma. The reasoning as stated in the dossier was: "the Applicant considers that it is unnecessary to single out and include prior history of exacerbations in the indication statement and that there is no single eosinophil level that defines the eosinophilic phenotype. The Applicant argues that efficacy was demonstrated across a range of baseline eosinophil levels, including in the <300/μL population. As such, an eosinophil cut-off is not included in the proposed indication. Of note, however, baseline blood eosinophil level and prior history of exacerbation are both potential predictors of benefit in patients to be prescribed benralizumab, and therefore, this evidence has been added to Section 5.1 of the proposed SmPC. This option is acceptable and is in line with the SmPC of similar products."[32]

DISCUSSION

In this study, we show that biomarkers are widely used in the selection of patients in the clinical programs of 119 recently approved medicines from 2018 to 2020 in Europe. In the SmPC of 52 (46%) approved medicines, 86 biomarkers for patient selection were mentioned in the clinical efficacy and safety information. Nevertheless, only for 26 medicines, the indication was restricted to the biomarker-positive population. Out of these 26 approvals, 11 were supported with main clinical studies in biomarker-positive and biomarker-negative populations, but for most (15 of 26) medicines, only biomarker-positive populations were included, because the used biomarkers had already been widely recognized and accepted before. Most dossiers were supported by RCTs ($n = 16$) and SATs ($n = 8$), the latter especially often for indications with predictive genetic or histological biomarkers. In two cases a more innovative basket trial design was applied.

A study of Gromova et al.[14] found an even higher use of biomarkers (65%, including surrogates) in the development of approved medicines when performing a keyword search in the complete EPARs, compared to our approach in which we manually screened specific sections of the SmPC. We confirm the wide use of biomarkers but add that only in a small proportion of the medicinal products the indication was eventually restricted to the population defined by the specific biomarker. Indication statements, however, often describe conditions that are defined by specific biomarkers in guidelines or clinical practice.

Unsurprisingly, the majority of products specifying biomarkers in the indication were for oncology treatment. Implementation of precision medicine in oncology treatment development has been very successful, building on an improved understanding of disease pathology. Biomarker-guided clinical trials have proven to be very effective, leading to many approved anticancer drugs targeting specific molecular targets and supported by the co-developed companion diagnostics.[15,33] Additionally, several products for rare genetic diseases were included in the in-depth analysis, including betibeglogene autotemcel for treatment of transfusion-dependent β- thalassemia, autologous *CD34+* cells encoding *ARSA* gene for treatment of metachromatic leukodystrophy, triple therapy with ivacaftor, tezacaftor, and elexacaftor for treatment of cystic fibrosis, onasemnogene abeparvovec for treatment of smooth muscular atrophy, and voretigene neparvovec for treatment of inherited retinal dystrophy. In such rare (mostly pediatric) diseases, biomarkers may provide a solution, because large long-term clinical trials are often not feasible.[34] However, our study did not show that biomarkers for patient selection were more often included in dossiers of orphan medicines.

Very few products in our study were approved based on novel biomarkers. The majority of the biomarkers included in the indication were biomarkers that were already known from literature and over 50% were present in the list of cleared or approved companion diagnostics provided by the FDA.[35–37] None of the biomarkers included in the indication of the selected products underwent approval through the Qualification of Novel Methodologies for Drug Development procedure initiated by the EMA[38] or through the Biomarker Qualification Program at the FDA.[39] This is not surprising, because qualification of the biomarkers through these procedures is not required for their use in medicines development. The fact that most of

the biomarkers in our study were not "novel," may explain why, in the majority of cases, only biomarker-positive populations were included in the clinical programs. Justification for solely including the biomarker-positive population in confirmatory studies was often not provided within the dossier. In case of "known" biomarkers, the CHMP usually followed the applicant's proposed indication and agreed with the studies' design and drawn conclusions. In some cases, however, the biomarker definitions were subject to a discussion and additional analyses of (sub) populations were requested. A precise and substantiated definition of biomarkers, including threshold setting to determine the target population is crucial, because both excluding a population that may benefit from the product as well as including a population that is likely not to benefit from the product is undesirable and unethical. Nevertheless, it should be noted that the EPAR is a curated document that may not contain extensive discussions that regulators may have shared in earlier versions of the assessment procedure reports. In case no major issues arose during the medicine's registration process, limited information on the biomarker development will be covered in the EPAR. For example, most of the biomarkers identified in the study of Maliepaard et al. (2022) were analytically validated to a reasonable extent for use in the clinical trials prior to their initiation and were often discussed with the regulators in the context of a scientific advice.[15]

The extent of discussions around the used biomarkers may not only be influenced by novelty of the biomarker, but also by type of biomarker and type of disease. Whereas presence or absence of, for instance, genetic mutations can be relatively straightforward, although, in some cases, different variations can be defined, establishing thresholds of continuous biomarkers is usually more complex.[40,41] In multifactorial diseases, it may be more appropriate to use biomarker panels, even further complicating definition and validation strategies. At the same time, this is an important reason why there are less biomarker-guided treatments for diseases for which etiology and drug targets are less straightforward as compared to oncology. Especially in these chronic multifactorial diseases, better use of biomarkers may support successful developments by optimizing patient selection and response to treatment.[42]

Similar to the use of novel biomarkers, the use of novel trial designs in the studied dossiers was limited. In most cases, RCTs provided main controlled data of a medicines' efficacy and safety, with the indication based on the population included in those trials. In a few approvals, however, additional analyses resulted in a different target population included in the indication than the total population studied in the trial. Some dossiers were supported by SATs which were considered to be acceptable, likely for ethical reasons in case of rare or severe diseases and/or late lines of treatment. Populations in these SATs were often selected based on a predictive genetic or predictive histological biomarker. In only two cases (entrectinib/larotrectinib), an innovative basket trial design was applied. These two treatments received a tumor-agnostic indication, where patients were selected based on genetic profile of the tumor rather than the localization.[43,44] The fact that innovative trial designs are not used for development of these medicines more often may be due to the challenges in the planning of these studies, but also in their regulatory assessment.[45]

A study of Vass et al.[46] showed that novel clinical trial methodologies are, however, the predominant "enabling technology" mentioned in recent EMA procedures, such as the Qualification of Novel Methodologies or Scientific Advice procedures and Innovation Task Force meetings. However, the issued discussed and insights gained during these procedures remain confidential. Nevertheless, it is anticipated that this will eventually translate into an increased representation of these methodologies in future marketing authorization dossiers. According to the same study, novel biomarkers are more prevalent hits in a PubMed search as compared to a search in the selected EMA procedures or clinical trial registrations.[46] One explanation could be that novel biomarkers are being investigated widely, but have not reached the clinical stage yet. Transparent communication and collaboration between regulators and biomarker developers is essential to move these early developments forward, by sharing information and increase common understanding of evidentiary standards that govern the use of biomarkers in medicine development programs.[47] Regulatory agencies, including the EMA, aim to advance research and uptake of innovative methods in medicines' development and regulatory evaluation, including biomarkers, as presented in the strategic goals in the EMA Regulatory Science Strategy to 2025.[48] Although the EMA's and the FDA's biomarker qualification programs are not required for biomarker use in medicine development, consortia focusing on biomarker and novel treatments development in disease areas with a high unmet medical need value obtaining this regulatory approval and sharing their obtained knowledge with the public.[49,50] Optimizing these procedures[51] and incentivizing different stakeholders, may stimulate broader uptake of precision medicine in the best interest of patients and health care in general.

Strengths and limitations

This study provides an in-depth review of biomarkers used for patient selection in recent centrally approved

medicines in Europe, including the characteristics of the biomarkers, what type of study designs were used in clinical programs, and why the biomarkers were included in medicines' indications or not. The results, however, should be considered in light of some limitations. This type of data extraction and analysis is vulnerable to selection bias, therefore data were extracted and discussed by multiple researchers to minimize subjectivity. EPARs are comprehensive documents comprising detailed information on medicines' regulatory authorization process. Nevertheless, earlier stage assessment reports or regulators' scientific advice reports may, in some cases, better capture discussions on biomarker-related decisions made in the early development phase.

CONCLUSION

Biomarkers are widely used for patient selection in recent medicines development, of which some are included in the medicines' indications. These are, however, often well-known biomarkers, and predominantly in the field of oncology. Very few products were approved in this timeframe based on novel biomarkers and innovative trial designs, leaving room for improvement regarding the approval of new precision medicines. Definitions of the biomarkers were mainly established before the clinical development. However, the discussions and adaptations requested concerning the biomarker cutoff values underline the importance of thorough justification of these definitions to include the right population for an optimal benefit–risk balance. Early collaboration between stakeholders leading to regulatory endorsement of biomarker-guided strategies may stimulate broader implementation of precision medicine.

AUTHOR CONTRIBUTIONS

E.B., V.S., H.J.L.H., and P.G.M.M. wrote the manuscript. E.B., V.S., J.W.M.K., and P.G.M.M. designed the research. E.B., V.S., and J.W.M.K. performed the research. E.B. analyzed the data.

FUNDING INFORMATION

This project has received funding from the Innovative Medicines Initiative (IMI) 2 Joint Undertaking under grant agreement no. 115974 (Biomarker Enterprise to Attack DKD; BEAT-DKD) and the Horizon Europe Research and Innovation Actions (HORIZON-HLTH-2022-TOOL-11-01 - Tools and technologies for a healthy society) undertaking under grant agreement no. 101095146 (Personalized Drug Response: IMplementation and Evaluation in CKD; PRIME-CKD). The Joint Undertaking receives support from the European Union's Horizon 2020 research and innovation program and European Federation of Pharmaceutical Industries and Associations (EFPIA) with JDRF. Any dissemination of results reflects only the author's view; the European Union, the Joint Undertaking, or the granting authority cannot be held responsible for any use that may be made of the information it contains. The funding sources did not have a role in the design, conduct, or analysis of the study.

CONFLICT OF INTEREST STATEMENT

E.B. received funding from the Biomarker Enterprise to Attack DKD (BEAT-DKD). V.S., H.J.L.H., and P.G.M.M. received funding from Personalized Drug Response: IMplementation and Evaluation in CKD (PRIME-CKD). H.J.L.H. is a member of the steering committees of the DAPA-CKD trial. Research grants are paid to his employer from AstraZeneca, Boehringer Ingelheim, Janssen, and Novo Nordisk. He is consultant to AstraZeneca, Bayer, Boehringer Ingelheim, Chinook, CSL Behring, DIMERIX, Eli-Lilly, Gilead, Janssen, Merck, Novartis, Novo Nordisk, AND Travere Therapeutics. J.W.M.K. declared no competing interests for this work.

DISCLAIMER

Any dissemination of results reflects only the authors' view; and may not be understood or quoted as being made on behalf of or reflecting the position of their institutions.

ORCID

Elisabeth Bakker https://orcid.org/0000-0002-3359-9588

REFERENCES

1. European Commission. Personalised medicine: Background, conference reports, publications and links related to personalised medicine. Accessed July 18, 2023. https://research-and-innovation.ec.europa.eu/research-area/health/personalised-medicine_en
2. Fountzilas E, Tsimberidou AM, Vo HH, Kurzrock R. Clinical trial design in the era of precision medicine. *Genome Med*. 2022;14:101. doi:10.1186/s13073-022-01102-1
3. FDA-NIH Biomarker Working Group. *BEST (Biomarkers, EndpointS, and Other Tools) Resource*. Food and Drug Administration and National Institutes of Health; 2016.
4. Abrahams E, Ginsburg GS, Silver M. The personalized medicine coalition. *Am J Pharmacogenomics*. 2005;5:345-355. doi:10.2165/00129785-200505060-00002
5. Hartl D, de Luca V, Kostikova A, et al. Translational precision medicine: an industry perspective. *J Transl Med*. 2021;19:245. doi:10.1186/s12967-021-02910-6
6. U.S. Food and Drug Administration. Enrichment Strategies for Clinical Trials to Support Approval of Human Drugs and Biological Products - Guidance for Industry. 2019. Accessed July

19, 2023. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/enrichment-strategies-clinical-trials-support-approval-human-drugs-and-biological-products
7. Wang J, Chang M. Innovative designs for biomarker-guided trials. In: Fang L, Su C, eds. *Statistical Methods in Biomarker and Early Clinical Development*. Springer; 2019:53-65. doi:10.1007/978-3-030-31503-0_4
8. Califf R. Biomarker definitions and their applications. *Exp Biol Med*. 2018;243:213-221. doi:10.1177/1535370217750088
9. European Medicines Agency. Innovation in medicines. Accessed December 5, 2022. https://www.ema.europa.eu/en/human-regulatory/research-development/innovation-medicines
10. European Medicines Agency. Qualification of Novel Methodologies for Medicine Development. Accessed February 27, 2023. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/qualification-novel-methodologies-medicine-development-0
11. U.S. Food and Drug Administration. Biomarker Qualification Program. Accessed December 05, 2022. https://www.fda.gov/drugs/drug-development-tool-ddt-qualification-programs/biomarker-qualification-program#:~:text=The%20mission%20of%20the%20CDER,and%20innovation%20in%20drug%20development
12. Bakker E, Hendrikse NM, Ehmann F, et al. Biomarker qualification at the European medicines agency: a review of biomarker qualification procedures from 2008 to 2020. *Clin Pharmacol Ther*. 2022;112:69-80. doi:10.1002/cpt.2554
13. Hendrikse NM, Llinares Garcia J, Vetter T, Humphreys AJ, Ehmann F. Biomarkers in medicines development-from discovery to regulatory qualification and beyond. *Front Med*. 2022;9:878942. doi:10.3389/fmed.2022.878942
14. Gromova M, Vaggelas A, Dallmann G, Seimetz D. Biomarkers: opportunities and challenges for drug development in the current regulatory landscape. *Biomarker Insights*. 2020;15:1177271920974652. doi:10.1177/1177271920974652
15. Maliepaard M, Nibi P, Nibi G, Pasmooij AMG. Evaluation of companion diagnostics in scientific advice and drug marketing authorization applications by the European medicines agency. *Front Med*. 2022;9:893028. doi:10.3389/fmed.2022.893028
16. European Medicines Agency. Download medicine data. Accessed December 5, 2022. https://www.ema.europa.eu/en/medicines/download-medicine-data#european-public-assessment-reports-(epar)-section022
17. Directorate-General for Health and Food Safety. Directive 2001/83/EC of the European Parliament and of the council of 6 November 2001 on the community code relating to medicinal products for human use. *OJEU*. 2001;311:67-128.
18. European Medicines Agency. European public assessment reports: background and context. Accessed January 4, 2023. https://www.ema.europa.eu/en/medicines/what-we-publish-when/european-public-assessment-reports-background-context
19. EUPATI. Special populations in clinical studies. Accessed February 17, 2023. https://toolbox.eupati.eu/resources/special-populations-in-clinical-studies/
20. World Health Organization. Anatomical Therapeutic Chemical (ATC) Classification. Accessed May 3, 2023. https://www.who.int/tools/atc-ddd-toolkit/atc-classification
21. European Medicines Agency. Imfinzi: EPAR – public assessment report. 2018. Accessed January 5, 2023. https://www.ema.europa.eu/en/documents/assessment-report/imfinzi-epar-public-assessment-report_en.pdf
22. European Medicines Agency. Mylotarg: EPAR – public assessment report. 2018. Accessed January 5. 2023. https://www.ema.europa.eu/en/documents/assessment-report/mylotarg-epar-public-assessment-report_en.pdf
23. European Medicines Agency. Vocabria: EPAR – public assessment report. 2020. Accessed January 5, 2023. https://www.ema.europa.eu/en/documents/assessment-report/vocabria-epar-public-assessment-report_en.pdf
24. European Medicines Agency. Staquis: EPAR – public assessment report. 2020. Accessed January 5. 2023. https://www.ema.europa.eu/en/documents/assessment-report/staquis-epar-public-assessment-report_en.pdf
25. European Medicines Agency. Zynquista: EPAR – public assessment report. 2019. Accessed January 5. 2023. https://www.ema.europa.eu/en/documents/assessment-report/zynquista-epar-public-assessment-report_en.pdf
26. European Medicines Agency. Lorviqua: EPAR – public assessment report. 2019. Accessed January 5, 2023. https://www.ema.europa.eu/en/documents/assessment-report/lorviqua-epar-public-assessment-report_en.pdf
27. European Medicines Agency. Alunbrig: EPAR – public assessment report. 2018. Accessed January 5, 2023. https://www.ema.europa.eu/en/documents/assessment-report/alunbrig-epar-public-assessment-report_en.pdf
28. European Medicines Agency. Mektovi: EPAR – public assessment report. 2018. Accessed January 5, 2023. https://www.ema.europa.eu/en/documents/assessment-report/mektovi-epar-public-assessment-report_en.pdf
29. European Medicines Agency. Ilumetri: EPAR - public assessment report. 2018. Accessed May 4, 2023. https://www.ema.europa.eu/en/documents/assessment-report/ilumetri-epar-public-assessment-report_en.pdf
30. European Medicines Agency. Besremi: EPAR – public assessment report. 2018. Accessed May 4, 2023. https://www.ema.europa.eu/en/documents/assessment-report/besremi-epar-public-assessment-report_en.pdf
31. European Medicines Agency. Fasenra: EPAR – public assessment report. 2017. Accessed May 4, 2023. https://www.ema.europa.eu/en/documents/assessment-report/fasenra-epar-public-assessment-report_en.pdf
32. European Medicines Agency. Braftovi: EPAR – public assessment report. 2018. Accessed January 5, 2023. https://www.ema.europa.eu/en/documents/assessment-report/braftovi-epar-public-assessment-report_en.pdf
33. Jørgensen JT. A paradigm shift in biomarker guided oncology drug development. *Ann Transl Med*. 2019;7:148. doi:10.21037/atm.2019.03.36
34. Bai JP, Barrett JS, Burckart GJ, Meibohm B, Sachs HC, Yao L. Strategic biomarkers for drug development in treating rare diseases and diseases in neonates and infants. *AAPS J*. 2013;2:447-454. doi:10.1208/s12248-013-9452-z
35. Cocco E, Scaltriti M, Drilon A. NTRK fusion-positive cancers and TRK inhibitor therapy. *Nat Rev Clin Oncol*. 2018;15:731-747. doi:10.1038/s41571-018-0113-0
36. Liu D. Cancer biomarkers for targeted therapy. *Biomark Res*. 2019;7:25. doi:10.1186/s40364-019-0178-7

37. U.S. Food and Drug Administration. List of Cleared or Approved Companion Diagnostic Devices (In Vitro and Imaging Tools). Accessed December 5, 2022. https://www.fda.gov/medical-devices/in-vitro-diagnostics/list-cleared-or-approved-companion-diagnostic-devices-in-vitro-and-imaging-tools
38. European Medicines Agency. Opinions and letters of support on the qualification of novel methodologies for medicine development. Accessed December 5, 2022. https://www.ema.europa.eu/en/human-regulatory/research-development/scientific-advice-protocol-assistance/novel-methodologies-biomarkers/opinions-letters-support-qualification-novel-methodologies-medicine-development
39. U.S. Food and Drug Administration. List of Qualified Biomarkers. Accessed December 5, 2022. https://www.fda.gov/drugs/biomarker-qualification-program/list-qualified-biomarkers
40. Subtil F, Rabilloud M. Estimating the optimal threshold for a diagnostic biomarker in case of complex biomarker distributions. *BMC Med Inform Decis Mak*. 2014;14:53. doi:10.1186/1472-6947-14-53
41. Woo SY, Kim S. Determination of cutoff values for biomarkers in clinical studies. *Precis Future Med*. 2020;4(1):2-8. doi:10.23838/pfm.2019.00135
42. Perco P, Pena M, Heerspink HJL, Mayer G, BEAt-DKD Consortium. Multimarker panels in diabetic kidney disease: the way to improved clinical trial design and clinical practice? *Kidney Int Rep*. 2018;14(2):212-221. doi:10.1016/j.ekir.2018.12.001
43. European Medicines Agency. Rozlytrek: EPAR – public assessment report. 2020. Accessed February 27, 2023. https://www.ema.europa.eu/en/documents/assessment-report/rozlytrek-epar-public-assessment-report_en.pdf
44. European Medicines Agency. Vitrakvi: EPAR – public assessment report. 2019. Accessed February 27, 2023. https://www.ema.europa.eu/en/documents/assessment-report/vitrakvi-epar-public-assessment-report_en.pdf
45. Collignon O, Gartner C, Haidich AB, et al. Current statistical considerations and regulatory perspectives on the planning of confirmatory basket, umbrella, and platform trials. *Clin Pharmacol Ther*. 2020;107:1059-1067. doi:10.1002/cpt.1804
46. Vass P, Akdag DS, Broholm GE, Kjaer J, Humphreys AJ, Ehmann F. Enabling technologies driving drug research and development. *Front Med*. 2023;10:1122405. doi:10.3389/fmed.2023.1122405
47. European Medicines Agency. EMA regulatory science to 2025: strategic reflection. 2020. Accessed February 02, 2023. https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/ema-regulatory-science-2025-strategic-reflection_en.pdf
48. Berman S, Siegel J. Biomarker qualification at the European Medicines Agency: a look under the Hood. *Clin Pharmacol Ther*. 2022;112:28-30. doi:10.1002/cpt.2609
49. Rasmussen DGK, Anstee QM, Torstenson R, et al. AFLD and NASH biomarker qualification in the LITMUS consortium - lessons learned. *J Hepatol*. 2023;78(4):852-865. doi:10.1016/j.jhep.2022.11.028
50. Personalized Drug Response: Implementation and Evaluation in CKD (Chronic Kidney Disease. WP4: Optimization of biomarker qualification procedures with regulatory agencies. 2023. Accessed July 20, 2023. https://prime-ckd.com/work-package-4/
51. European Medicines Agency. EMA multi-stakeholder workshop on qualification of novel methodologies. 2023. Accessed July 20, 2023. https://www.ema.europa.eu/en/events/ema-multi-stakeholder-workshop-qualification-novel-methodologies

How to cite this article: Bakker E, Starokozhko V, Kraaijvanger JWM, Heerspink HJL, Mol PGM. Precision medicine in regulatory decision making: Biomarkers used for patient selection in European Public Assessment Reports from 2018 to 2020. *Clin Transl Sci*. 2023;16:2394-2412. doi:10.1111/cts.13641