Health Policy xxx (2020) xxx–xxx

Contents lists available at ScienceDirect

Health Policy

journal homepage: www.elsevier.com/locate/healthpol

Review of Relative effectiveness assessments (REAs) of pharmaceuticals at the European network for health technology assessment(EUnetHTA): A first step towards a consolidated European perspective on comparative effectiveness & safety?

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ARTICLE INFO

Article history:
Received 6 January 2020
Received in revised form 3 April 2020
Accepted 22 June 2020

Keywords:
EUnetHTA
Relative effectiveness assessment
Clinical data development
Health technology assessment
Pharmaceuticals

ABSTRACT

Objectives: REAs from Joint Action (JA1–3) were reviewed and compared versus Health Technology Assessments (HTA) in France, Germany, UK, Italy.
Methods: EUnetHTA REAs published until end of 2019 were identified. Leveraging information derived from the HTA bodies' website key process (population; timing; national HTA bodies involved) and content characteristics (evidence base; comparative therapy, endpoints, subgroups) were determined and compared against national appraisals.
Results: All twelve pharmaceutical EUnetHTA assessment finalized until end of 2019 were included with Ustekinumab being the most recent (October 2019) and Pazopanib the first assessment (September 2012). In all but three assessments EUnetHTA's assessment did not cover the full EMA indication. Since JA3 time intervals between EMA approval and EUnetHTA assessment were < 80 days. Number of (co-)authoring HTA bodies ranged between 2 (in 6 REAs) and > 10 (Pazopanib). EUnetHTA did consider non – RCT evidence in 7 procedures; take a rather inclusive approach regarding appropriate comparative treatments; approach endpoints less restrictively than e.g. the German IQWiG/G—BA; not apply a predetermined set of subgroups analyses. In seven REAs, national appraisal showed inhomogeneities across the 4 countries. National appraisals for Sotagliflozin and Ustekinumab were not yet available.
Conclusions: A joint European HTA assessment has the potential to address the challenge of heterogeneity across the various national European HTA bodies and to determine joint European clinical development data standards that are aligned with regulatory requirements.

1. Introduction

Health Technology Assessment (HTA) is a common feature across European countries. All involved national institutions aim for an optimization of health care costs and respective outcomes. However, applied HTA procedures and related appraisals largely differ across the various European Countries [1]. To facilitate European cooperation on HTA, the European Union (EU) has been funding the Joint Action European Network for Health Technology Assessment (EUnetHTA) for more than two decades. EUnetHTA is a network of government appointed organisations, relevant regional agencies, and non-for-profit organisations that produce or contribute to HTA across Europe. Relative Effectiveness Assessments (REA) by EUnetHTA determine whether an intervention does more good than harm, compared to one or more intervention alternatives [2]. In particular four assessment domains are considered within the assessment: i) Health Problem and Current Use of Technology; ii) Description and technical characteristics of technology; iii) Safety; iv) Clinical Effectiveness. All other domains (costs and economic effectiveness; ethical analysis, organisational aspects, patient and

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https://doi.org/10.1016/j.healthpol.2020.06.013
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social aspects; legal aspects) as well as the final appraisal remain within the national authority.

Despite the wide range of EUnetHTA's related activities including joint Relative Effectiveness Assessments (REAs) [2], early dialogues with the industry [3], and the development of a conceptual framework to structure and further align European HTA assessments [4,5] uptake of EUnetHTA's REAs among the national HTA bodies has been limited so far [6]. Legal and administrative hurdles as well as concerns regarding quality, timeliness and reliability of available EUnetHTA assessments are impacting national uptake of EUnetHTA assessments. Powerful national HTA bodies such as the 'Haute Autorité de Santé' (HAS) in France [7], the 'Federal Joint Committee' (G-BA) in Germany [8], the 'Agenzia Italiana del Farmaco' (AIFA) in Italy [9], or the 'National Institute for Health and Care Excellence' (NICE) in the UK [10], have conducted their own assessments and appraisals, often revealing considerable differences across countries.

To further strengthen collaboration between the 81 national or regional European HTA institutions that are currently included in EUnetHTA [11] and to address some of the shortcomings of the current project-by-project interaction, the European Commission has developed a proposal for an EU regulation on HTA [12]. This regulation aims to foster an increased collaboration across EU member states regarding clinical and scientific components, a joint focus on quality, transparency, and timely output, and an increased exchange among European HTA bodies. However, while countries are requested to take EUnetHTA assessments into consideration, the final appraisal as well as pricing and reimbursement decision will remain with the involved national bodies.

The proposed regulation is still in the legislative process involving both the European Council and the European Parliament. Also, key countries including France, Germany, Czech Republik and Poland have filed a subsidy complain requesting a stronger reflection and maintenance of specific national requirements in the HTA process. Nevertheless, it seems clear that the role of EUnetHTA in shaping a joint European perspective on HTA assessments is continuously evolving. Compared to the vast experience of the key national HTA bodies and the multiple HTA processes they have orchestrated the number of EUnetHTA REAs is still limited. To date 12 assessments have been finalized and published. Five REAs are related to EUnetHTA Joint Action (JA) 3, six to the previous JA 2 period and one to JA1. Another eight REAs are in progress.

With this analysis, we aimed to systematically review published EUnetHTA REAs and to compare findings with the outcomes of the respective national HTA appraisals in France, Germany, Italy, and the UK.

2. Methods

This analysis includes all published EUnetHTA REAs that were finalized before December, 31st, 2019. EUnetHTA's homepage (https://www.eunethta.eu) was used to obtain all available documents. In addition, regulatory information such as timing of the approval, details of the indication statement, or specific benefit – risk considerations were derived from the documents available on the European Medicine Agency (EMA) website: https://www.ema.europa.eu/en.

The criteria for the selection of countries were i) size of the market and ii) representation of the different HTA systems across Europe. France, Germany, Italy and UK are representing the 4 largest economies across Europe. In addition, UK leverages the cost-effectiveness assessments while France a Germany a separating the assessment of additional benefit from the subsequent price negotiations. Finally, Italy has the regulatory and HTA authority within one organisation (AIFA) which is similar to Norway and Portugal. Details of the national appraisals were derived from the respective websites: France: www.has-sante.fr, Germany: https://www.g-ba.de, Italy: https://www.gazzettaufficiale.it, and UK: www.nice.org.uk.

For both the EUnetHTA assessment and the national appraisals key process and content characteristics were systematically analysed for each indication/ medicine.

The *process review* included the:

i) Population of EUnetHTA's assessment and the four national appraisals i.e. the patients and indication that EUnetHTA and the national bodies focussed on
ii) Timing of EUnetHTA's assessment and the national appraisals relative to the timing of EMAs decision on marketing authorisation
iii) Number of HTA bodies involved in EUnetHTA's assessment.

The *content review* included:

i) Evidence Base: We examined to what extent evidence beyond RCTs was leveraged within the clinical section of EUnetHTA's REAs. In particular, we searched for the usage of single arm trials and indirect evidence such as indirect treatment comparisons (ITC), and/or network meta-analysis (NMA).
ii) Comparative treatments: We examined the acceptance of off-label comparators within EUnetHTA's assessments and the inclusion of comparators other than that provided within the submitted clinical trial data.
iii) Endpoints: Endpoints included in the assessment and in the concluding value considerations were analysed. A key focus was EUnetHTA's perspective on clinical relevance and surrogate endpoints. Furthermore, we explored to what extent EUnetHTA's approach to endpoints evolved over time e.g. in the oncology and diabetes assessments.
iv) Subgroups: Analysis of patient subgroups does frequently occur in HTA assessments. Selection of subgroups within the EUnetHTA REAs was analysed and repeated patterns of included subgroups were searched.
v) Finally, the results of the national appraisals and EUnetHTA's concluding comments were identified and summarized. Colour coding was applied for the national appraisals with green representing an ASMR < 4 (France), and additional benefit assigned by the G-BA (Germany), Class H or A and innovation status in Italy [16] and a positive recommendation by NICE and red any other appraisal. As EUnetHTA does provide an assessment rather than an appraisal no colour coding was applied to EUnetHTA concluding comments. However, positive and negative trends within EUnetHTA's conclusions were identified and described.

All analyses were based on all available JA1, JA2, JA3 pharmaceutical REAs. However, Pazopanib, the very first assessment was excluded from our analysis of i) timelines and ii) the number of involved HTA bodies. As it was the very first EUnetHTA REA both, the large number of HTA bodies involved in authoring and reviewing the document and the timing of the assessment does not reflect standard EUnetHTA practice within JA2 and JA3.

Furthermore, the Varicella - zoster Vaccine was excluded from the assessment of timelines as the manufacturer considerably postponed the market introduction of the medicine in the various European markets which explains the lengthy time interval between EMA approval and availability of the various HTA assessments/appraisals.

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Table 1
Medicines included in the Analysis.

Medicine	Licensed Indications	Population covered by REA	EMA Approval	EUnetHTA assessment (JA#)	EUnetHTA (Co-)author Country	Appraisals in France, Germany, Italy, UK
Ustekinumab	Moderate to severe 2nd line or 1st line with contraindications vs other treatments: Crohn's Disease and Ulcerative Colitis	Moderate to severe 2nd line or 1st line with contraindications vs other treatments: Ulcerative Colitis	July 25th '19(Jan 15th '09)	Oct 22nd '19(JA 3)	Croatia (Poland/ Sweden)	National appraisals not yet available
Sotagliflozin	Type 1 Diabetes Mellitus; Insulin failure; BMI ≥ 27 kg/m^2	Equals Indication	Apr 26th '19	Jun 7th '19(JA3)	Sweden (Netherlands; Ireland)	National appraisals not available; product not launched yet
Alectinib	2nd and 1st line treatment NSCLC ALK+	1st line treatment NSCLC ALK+	Dec 18th' 17(Feb 16th' 17) *	Feb 23rd '18(JA3)	Sweden (Austria/ Croatia)	National appraisals available
Midostaurin**	Acute Myeloid Leukaemia FLT3+; Newly Diagnosed; Mastocytosis	Acute Myeloid Leukaemia FLT3+; Newly Diagnosed	Sep 18th' 17	Nov 6th '17(JA3)	Finland (Norway)	National appraisals available
Regorafenib	Colorectal Cancer; Gastrointenstinal Stroma Tumours; Hepatocellular Carcinoma 2nd line	Hepatocellular Carcinoma 2nd line (only Child Pugh Score A & ECOG 0/1)	Aug 2nd' 17(Aug 26th '13) *	Oct 19th '17(JA3)	France (Protugal)	Appraisals in France, Italy, UK available; Medicine was withdrawn from German market
6 new oral Medicines	Hepatitis C (Genotypes are specified per product)	Equals Indication	Various Timepoints	Jun 17th '15(JA2)	Belgium; Croatia; Italy (Austria)	National appraisals available
Vorapaxar	Reduction of atherothrombotic events in patients with Myocardial Infarction and symptomatic peripheral arterial disease	Reduction of atherothrombotic events in patients with Myocardial Infarction	Jan 19th' 15(Jun 23rd' 17) +	Nov 18th '15(JA2)	France (Slovakia)	Only French appraisal available
Ramucirumab	Mono / Combination therapy in 2nd line gastric/ gastro-oesophageal carcinoma; Combination Therapy in Colorectal Cancer; NSCLC	Combination therapy in 2nd line gastric/ gastro-oesophageal carcinoma	Dec 19th '14++	Mar 23rd '15(JA2)	Norway (Croatia)	National appraisals available
Sorafenib**	Hepatocellular Carcinoma; Renal Cell Carcinoma; Locally Advanced or metastatic Thyroid Carcinoma	Locally Advanced or metastatic Thyroid Carcinoma	May 23rd '14(Jul 19th' 06) *	Mar 17th '15(JA2)	Italy (Portugal)	National appraisals in France, Italy, UK available; Medicine introduced prior to German AMNOG law
Canagliflozin	Monotherapy and Combination therapy in Type 2 Diabetes Mellitus	Combination therapy	Nov 15th '13	Feb 24th '14(JA2)	Croatia; Finland; Italy	National appraisals available
Varicella – zoster Vaccine	Prevention: Herpes Zoster; Postherpic Neuralgia	Equals Indication but people with compromised immunity excluded from trials	May 19th '06	Sept 17th '13(JA2)	Netherlands (Italy)	National appraisals in France and Italy available; Medicine introduced prior to German AMNOG law
Pazopanib	1st / 2nd line Advanced Renal Cell Carcinoma; Soft-tissue Sarcoma	1st / 2nd line Advanced Renal Cell Carcinoma	June 14th' 10 (July 1 st '13) &	Sep '12(JA1)	> 10 authors	National appraisals in France, Italy, UK available; Medicine introduced prior to German AMNOG law

* Time of initial marketing authorization; ** Orphan Designation; *** Direct Acting Antiviral Agents; + Withdrawal of Marketing Authorization; ++ Mono- and Combination Therapy were both part of the initial marketing authorization; & Full approval (initially conditional approval); && Marketing Authorization Holder; #Joint Action.

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3. Results

Altogether 12 pharmaceutical REAs were conducted by EUnetHTA until end of 2019 and included in this analysis. They are displayed in Table 1. Ustekinumab, Sotagliflozin, Alectinib, Midostaurin, and Regorafenib were conducted under EUnetHTA Joint Action 3 (JA3). The others (6 Direct Acting Antivirals, DAA in Hepatitis C, Vorapaxar, Ramucirumab, Sorafenib, Canagliflozin, Varicella – zoster Vaccine) related to EUnetHTA's JA2, and to JA 1 (Pazopanib). Sotagliflozin has not yet been launched in the European Markets despite availability of a respective EMA Marketing Authorisation [24].

Eleven procedures covered therapeutic medicines. The Varicella – zoster Vaccine for the Prevention of Herpes Zoster and Postherpic Neuralgia was the only vaccine with a REA. Six REAs (50 %) included Oncological Conditions. Other disease areas were: Diabetes (2 REAs), Hepatitis C (Direct Acting Antivirals, DAA), Atherothrombotic Events, Herpes Zoster Vaccine and Ulcerative Colitis with one REA each.

3.1. Process characteristics

3.1.1. Population

EUnetHTA's focus did match EMA's indication in Sotagliflozin, the Varicella – zoster Vaccine, and the 6 medicines in Hepatitis C. In Ustekinumab, Alectinib, Regorafenib, Ramucirumab, Vorapaxar, Canagliflozin and Sorafenib EUnetHTA assessed only part of the licensed indications. Midostaurin and Pazopanib also have additional indications (Mastocytosis and Soft-tissue Sarcoma) that were approved by EMA at the same time of the main indication (Acute Myeloid Leukaemia and Renal Cell Carcinoma) but were not within the scope of EUnetHTA's assessment. Vorapaxar's marketing authorization was withdrawn in 2017. In Regorafenib the clinical trial population only included ECOG 0/1 patients and Child Pugh Score A and in the Varicella – zoster Vaccine patients with compromised immunity were excluded from the clinical trial. In both medicines EUnetHTA focussed on the clinical trial evidence.

In France the population of HAS appraisals did match the respective indication. The same applies to Germany. However, Pazopanib, the Varicella – zoster Vaccine and Sorafenib received marketing authorization prior to the German AMNOG law, Vorapaxar was not launched in Germany and Regorafenib was withdrawn from the German market. In Italy and the UK no Vorapaxar appraisals were available. In the UK also the Varicella – zoster Vaccine and Pazopanib 2nd line appraisals are missing (see Fig. 2).

3.1.2. Timing

Pazopanib (first EUnetHTA assessment; 810 days between EMA approval and EUnetHTA assessment) and the Varicella – zoster Vaccine (2678 days between EMA approval and EUnetHTA assessment; the manufacturer delayed introduction of medicine into the market) were not included in the analysis of REA timing. Time between EMA approval and EUnetHTA assessment (national appraisals, respectively) of the remaining 10 REAs ranged between 42 [Sotagliflozin] and 298 [Sorafenib] days; (France 163 [Alectinib] and 376 [Sorafenib]; Germany 185 [Alectinib] and 293 [Canagliflozin]; UK 222 [Canagliflozin] and 1538 [Sorafenib]; Italy 107 [Vorapaxar] and 1413 [Sorafenib]) Fig. 1 .

3.1.3. HTA bodies involved

Excluding the first REA on Pazopanib, which was authored and reviewed by a multitude of HTA bodies, a total of 25 countries and 43 HTA bodies were actively involved in writing and reviewing the documents. EUnetHTA's (co-) author team consisted of 2 (Midostaurin; Regorafenib; Vorapaxar; Ramucirumab; Sorafenib; Varicella – zoster Vaccine), 3 (Ustekinumab, Sotagliflozin; Alectinib; Canagliflozin) and 4 national HTA bodies (Hepatitis C). Number of dedicated EUnetHTA reviewers ranged between 5 (Ustekinumab, Canagliflozin, Sorafenib, Ramucirumab, Alectinib, Sotagliflozin) and > 10 (Hepatitis C products and Pazopanib). Some countries participated with more than one HTA body in writing and reviewing the assessments: Austria, Belgium, Croatia, Hungary, Italy, Latvia, Netherlands, Norway, Spain. The number of national HTA bodies involved in EUnetHTA's assessments was highest in Spain. Altogether, 7 Spanish HTA bodies provided input into the reviewed 12 assessments.

3.2. Content characteristics

An overview of comparative content characteristics covered in our analysis is provided in Table 2.

3.2.1. EUnetHTA's evidence base

Submissions by the Marketing Authorization Holder (MAH) are the basis for the assessment in all but one of the REAs. In the assessment of the six new Hepatitis C medicines EUnetHTA relied only on published information. Some of the REAs (Alectinib; Midostaurin; Regorafenib; Vorapaxar) have a subsection titled 'Description of Evidence Used'. In other REAs this information is provided not as a subsection but as a separate table (e.g. Ramucirumab). However, some of the REAs such as the recent REA on Sotagliflozin does not provide a separate overview on included evidence.

Since JA3 EUnetHTA always considered information derived from a systematic literature review. Frequently the GRADE (The Grading of Recommendations Assessment, Development and Evaluation) methodology is leveraged to categorize the retrieved evidence [27]. In some of the JA2 assessments the literature review was missing or conducted non-systematically (Varicella – zoster Vaccine and Pazopanib). In Midostaurin, Hepatitis C and Pazopanib EUnetHTA included single arm clinical trial evidence. In the Varicella – zoster Vaccine patients from a non-randomised safety substudy were included. Real World Data were not included as source of clinical evidence in any of the REAs.

Indirect treatment comparisons (ITCs) were quite frequently leveraged by EUnetHTA. In Ustekinumab, Sotagliflozin and Alectinib EUnetHTA reviewed the Network Metanalyses (NMAs) that were provided by the company. In Midostaurin, Hepatitis C, Ramucirumab, Canagliflozin, and Pazopanib EUnetHTA conducted ITCs (NMAs, respectively) on their own and included the findings in their assessment. The Bucher method [15] was referenced in 4 of the 12 assessments (33 %). Among the four national HTA bodies only the UK leveraged indirect evidence (3 appraisals) and a metaanalysis (1 appraisal).

Comparing EUnetHTA's evidence base to the four national HTA bodies reveals that EUnetHTA has a more inclusive approach to evidence than e.g. the German HTA bodies G-BA and IQWiG. Indirect Treatment Comparisons and Single Arm Trials are included and considered as an element of evidence in EUnetHTA's REAs.

3.2.2. Comparative treatments

EUnetHTA does consider EMA documents, manufacturer submissions, and relevant clinical and EUnetHTA guidelines for the determination of comparative treatments but does not yet have a standard approach to determine the comparative therapy. In the assessment of Ramucirumab, EUnetHTA included off label treatments: Paclitaxel, Docetaxel, Irinotecan are not approved for second line treatment of gastric/ gastro-oesophageal carcinomas indicating that EUnetHTA is including clinical practice considerations in addition to regulatory approval status in their comparator selections.

In 8 (67 %) of the assessments, EUnetHTA reached beyond the clinical trial comparators of the investigational drug and

Table 2
Content Review of EUnetHTA REAs and main differences vs national appraisals in France (F), Germany (G), UK, Italy (I)*.

Medicine	Evidence Base		Comparator		Endpoints Driving Value Considerations		Subgroups Defined by HTA Body	
	EUnetHTA	Appraisals F, G, UK, I	EUnetHTA	Appraisals F, G, UK, I	EUnetHTA	Appraisals F, G, UK, I	EUnetHTA	Appraisals F, G, UK, I
Ustekinumab	1 RCT vs Placebo; NMA	n.a.	Adalimumab[##] Infliximab[##]; Golimumab; Vedolizumab; Tofacitinib	n.a.	Clinical Response Clinical Remission Mucosal (combination of endoscopic and histological) Healing	n.a.	Non Biologic Failure Biologic Fail-ure	n.a.
Sotagliflozin	6 RCTs vs Placebo; NMA	n.a.	Placebo Empagliflozin Dapagliflozin	n.a.	EUnetHTA does differentiate crucial vs important endpoints. No endpoint is driving value	n.a.	No	n.a.
Alectinib	1 RCT vs Critotinib; ITC & NMA	F, G, UK: only RCT	Crizotinib; Ceritinib	UK, G: suggested only Crizotinib	PFS; CNS Progression; Overall Safety Profile; QoL; OS considered immature	F, UK: PFS; CNS Progression G: CNS Progress I: Mature OS data requested	No	No
Midostaurin	1 RCT vs Chemotherapy; Single Arm Trial; ITC	F, G: only RCT	Standard Induction and Consolidation Chemotherapy	F, UK: no differences; G: Orphan Designation	OS; Secondary outcomes supportive (Event Free Survival; Disease Free Survival; Complete Remission Rate; Cumulative Incidence of Relapse)	F, G: OS key value driver UK: OS and Event Free Survival	Effect in continuation therapy unclear; data in elderly patients needed	F, G: impact of stem cell transplant unclear
Regorafenib	1 Clinical Trial Regorafenib vs BSC	F, UK: same evidence base	BSC/ Palliative Care	F, UK: Same comparator	Modest OS gain (2.8 months); worsened safety	UK: also referenced PFS benefit	Trial only included patients with preserved general state	F, UK share same concerns
Hepatitis C: six new medicines**	[+]49 Clinical Trials including single arm trials; NMA by EUnetHTA	F, G, UK: included Single arm trials. UK: Metaanalysis	Various Hepatitis C Medicines	Various Hepatitis C Medicines	Sustained Virologic Response (week 12 & 24); Overall Safety Profile	F: also leveraged term 'cure' G: some effects were considered 'dramatic' I: not all medicines assessed for innovation status	Genotype and Treatment line were differentiated	Genotype and Treatment line were differentiated
Vorapaxar	1 RCT	F: 1 RCT	Clopidogrel; ASS; Prasugrel; Ticagrelor	F: Same Comprators	Improvement in Morbidity (MIs);	F: Reduction in atherothrombotic events (composite principal endpoint); Greater incidence in haemorrhagic events	May be used if no previous MI, stroke, or TIA; not receiving Ticagrelor or Prasugrel	F: Patients with history of CVA or TIA to be excluded

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Table 2 (*Continued*)

Medicine	Evidence Base		Comparator		Endpoints Driving Value Considerations		Subgroups Defined by HTA Body	
	EUnetHTA	Appraisals F, G, UK, I	EUnetHTA	Appraisals F, G, UK, I	EUnetHTA	Appraisals F, G, UK, I	EUnetHTA	Appraisals F, G, UK, I
Ramucirumab[#]	1 RCT Ramu-cirumab vs Placebo; ITC	F,G: 1 RCT only UK: NMA	[++]Paclitaxel Docetaxel Irinotecan	F, UK: included also FOLFIRI; G: Physician's Choice UK: comment on Lenvatinib	Mortality data not robust; Increased risk of bleeding Overall Survival; Secondary outcomes supportive (PFS, ORR) PFS positive; AEs trending negative; Uncertainties: OS, secondary endopints	F, G: OS (2.3 months); increase in AEs G: Increase in QoL UK, F: PFS positive F: Safety and QoL negative UK: OS likely, extent uncertain	No [#]	F, UK separately considered HER2 pos patients F: selection of symptomatic fast progressors
Sorafenib	1 RCT Sora-fenib vs Placebo	UK does include Lenvatinib trial	Placebo (BSC)	G: Orphan Designation			Evidence Gap: > 75 years; dialysis, Child Pugh C, advanced tumor	
Canagliflozin	3 RCTs; ITC and Simulations	UK included NMA	Multiple Comparators	G: most restrictive regarding comparator selection	HbA1C; Cholesterol Levels; No information on mortality and long term outcome;	F, UK: HbA1C included G: Definition of Hypoglycaemia was criticized; HbA1C not relevant ot patients	Dual Therapy Triple Therapy Add on to Insulin	Dual Therapy Triple Therapy Add on to Insulin
Varicella – zoster Vaccine	2 finalized trials	1 RCT; Retrospective observational studies; Open label follow up studies	Placebo	F: Placebo	Incidence of Herpes Zoster and Post-herpectic Neuralgia	Incidence of Herpes Zoster	Age as risk factor for AEs	Age > 75 and immunocom-promised patients not recommended
Pazopanib	1 RCT Pazopanib vs Placebo; 2 single arm trials; ITC	F: lack of Head to Head evidence vs active comparator UK: ITC	1st line: Sunitinib; Aldesleukin; Bevacizumab; Interferon; BSC 2nd line: Sorafenib; BSC	UK covered only 1st line treatments	PFS extension OS and QoL impact inconclusive	UK: Increase in PFS and OS likely, uncertainty regarding magnitude	First vs Second Line	First vs Second line

AE Adverse Events; ASS Acetylsalicylic Acid; BSC Best Supportive Care; CNS Central Nervous System; CVS Cerebral Vascular Event; ITC Indirect Treatment Comparison; MI Myocardial Infarction; n.a. not applicable; NMA Network Metaanalysis; ORR Objective Response Rate; OS Overall Survival; PFS Progression Free Survival; QoL: Quality of Life; RCT Randomised Controlled Clinical Trial; REA Relative Effectiveness Analysis; TIA Transient Ischaemic Attack.
[*] Only Partial Information on Italy available; [**] EUnetHTA conducted one joint assessment; national appraisals were conducted as single technology assessments; [#]EUnetHTA's scope only included combination therapy i.e. Ramucirumab with Paclitaxel; National appraisals also covered Ramucirumab monotherapy, [##] Including available biosimilars; [+]Data derived from literature by EUnetHTA; [++] All three medicines are off-label comparators.

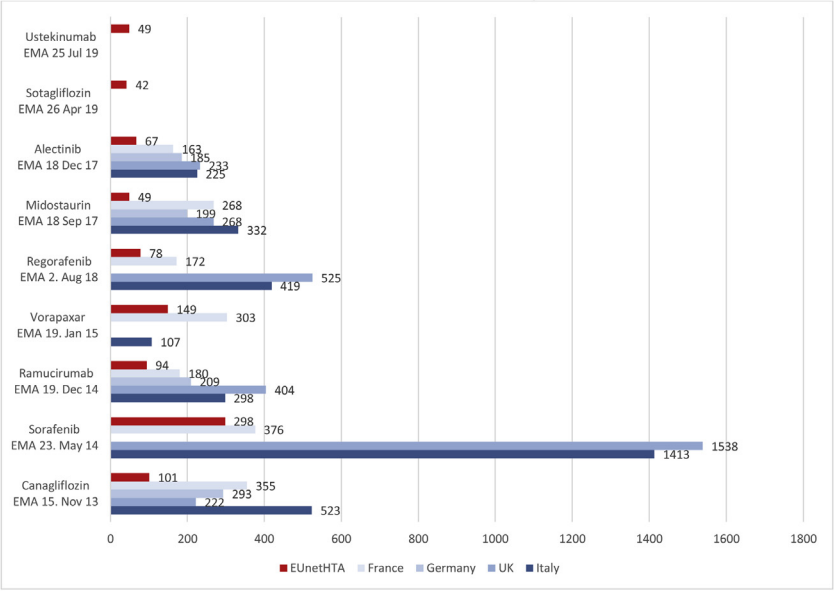

Fig. 1. Days between EMA approval and publication of assessment/ appraisal.

Medicines	Concluding EUnetHTA Value Comments	France	Germany	Italy*	UK
Ustekinumab	Trend positive in non-biologic failure; Trend no benefit in biologic failure: *Effective regarding clinical response, clinical remission and mucosal healing versus Placebo; Uncertainty in long term efficacy (> 1 year); NMA Non-biologic failure population: higher odds for clinical response; clinical remission and mucosal healing vs Placebo, Golimumab, Adalimumab; statistical difference in clinical response vs Infliximab and Tofacitinib; no statistically significance in clinical response, clinical remission and mucosal healing vs Vedolizumab. NMA Biologic Failure Population: all comparisons for effectiveness versus any active treatment were non-significant.*	*Appraisals Not Available*			
Sotagliflozin	Trend no benefit: *NMA vs Empagliflozin & Dapagliflozin: Quote: 'it is of note that neither dose of Sotagliflozin was ranked in first position for any of the outcomes included in the NMA'*	*Appraisals Not Available*			
Alectinib	Trend positive: *Substantial and significant PFS; Delay of CNS Progression of high clinical relevance. OS immature; clinically meaningful QoL improvement; Overall superior safety profile vs Ceritinib*				
Midostaurin	Trend positive: *Midostaurin considered more effective vs Chemo alone. Safety profile comparable; further research required in older population; Lack of comparator in FLT' patients*				
Regorafenib	Trend including positive and negative aspects: *Modest gain in OS (+2.8 months) must be seen in view of the worsened safety profile. Patients in the RESORCE trial only partially reflect indication.*		*Medicine withdrawn from Market*		
6 new oral medicines	Trend positive: *The main message is that high efficacy rates combined with a very acceptable safety profile can be achieved in most subgroups*				
Vorapaxar	*Trend including positive and negative aspects: Vorapaxar seems to improve CV morbidity mainly MI. In terms of safety it presents and increased risk of bleeding.*		*Medicine not submitted to G-BA*	*Class not determined*	*No Guidance available*
Ramucirumab	Trend positive: *OS (2.3 months) is considered clinically relevant for patients with poor prognosis; PFS and ORR support OS benefit. QoL maintained for a longer duration. Adverse event differences not statistically significant*				
Sorafenib	*Trend including positive and negative aspects: Clinical benefit of 5 months PFS may be considered clinically relevant; OS data lacking; RR benefit only modest. AEs likely to have negative impact on QoL. Lack of adequate comparator makes REA assessment challenging*		*Medicine introduced prior to AMNOG*		
Canagliflozin	*Trend including positive and negative aspects: Effects on surrogate endpoints (HbA1C; weight; blood pressure) seem to be at least as favorable as comparators and may be even more effective. Increases in LDL and HDL cholesterol. Insufficient evidence regarding long-term outcomes and mortality. Generally, well tolerated. Long term safety data needed*				
Varicella – zoster Vaccine	*Trend including positive and negative aspects: Varicella – zoster Vaccine is more effective than placebo. Age is a risk factor for severe adverse events*		*Medicine introduced prior to AMNOG*		*No Guidance available*
Pazopanib	*Trend positive:* Pazopanib extends PFS. Different opinions regarding surrogacy of PFS for OS in Renal Cell Carcinoma. Insufficient evidence for OS and QoL		*Medicine introduced prior to AMNOG*		

Fig. 2. HTA appraisals in France, Germany, Italy and UK. Green: ASMR ≤ 4 (France); Additional Benefit (Germany); Class H or A categorization in Italy; Recommended by NICE (UK); Pale Green: positive ratings with restrictions or only in subpopulations; Red: Any other appraisal; White: Appraisal not available (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article).
* Innovation Status according to new AIFA framework: Alectinib in 1st line NSCLC; Midostaurin in AML; 6 medicines in Hepatitis C; Regorafenib has conditional innovation for HCC which does not qualify for innovation fund.

included additional indirect comparisons and their respective clinical trial data: Ustekinumab was compared vs active comparators (Infliximab; Vedolizumab; Tofacitinib; Golimumab; Adalimumab); Sotagliflozin vs Empagliflozin and Dapagliflozin; Alectinib vs Ceritinib; Midostaurin vs Daunorubicin; the DAAs vs various comparative medicines in Hepatitis C; Ramucirumab vs Docetaxel and Irinotecan; Canagliflozin vs various antidiabetic regimes; Pazopanib vs a variety of treatments in renal cell carcinoma.

Comparator selection within the national appraisals is heterogeneous. E.g. in Alectinib Germany and UK only included Crizotinib while France also considered Ceritinib. In Canagliflozin GLP-1 analogues or DPP-4 inhibitors such as Sitagliptin are included in France and the UK while appropriate comparators in Germany are limited to Metformin, Sulfonylureas, and Insulin. In Germany regulatory approval is a key criterion for the determination of the comparative therapy.

3.2.3. *EUnetHTA's approach to endpoints*

EUnetHTA's perspective on endpoints is evolving. While the first diabetes assessment (Canagliflozin) included a variety of endpoints the recent assessment of Sotagliflozin separated 'crucial endpoints' from 'important endpoints', thus clearly prioritizing e.g. micro/ macrovascular complications; mortality endpoints, QoL over surrogate endpoints such as HbA1C, blood pressure or body weight.

In oncological conditions, the most important outcome seems overall survival with a median gain of 2.8 months (Regorafenib)

and 2.3 month (Ramucirumab) being considered clinically relevant by EUnetHTA.

Progression free survival (PFS) and other morbidity endpoints were included in all oncological assessments. While in the first assessment of Pazopanib different opinions within EUnetHTA regarding the surrogacy of PFS for OS were mentioned, time to central nervous system progress including the 'response assessment for neuro-oncology' (RANO) criteria in Alectinib and 5 months of PFS gain in Sorafenib were considered of high clinical relevance by EUnetHTA. Different opinions within EUnetHTA regarding the surrogacy of Progression Free Survival for Overall Survival were mentioned in the Pazopanib assessment.

Quality of Life is considered highly relevant, but data availability is often limited within the clinical trials which was repeatedly challenged by EUnetHTA.

Adverse events were included in all assessments and safety concerns impacting the overall value considerations were mentioned for Regorafenib, Vorapaxar and in elderly patients in the Varicella – zoster Vaccine. Safety as a positive driver of value was mentioned in the assessment of Alectinib and in Hepatitis C. The clinical relevance of elevations of blood lipid levels in Canagliflozin remained unclear.

Within the national appraisals UK and France take a more inclusive approach and always take primary clinical trial endpoints into consideration for their appraisal. In Germany HbA1C (Canagliflozin), PFS and ORR are often not considered relevant to patients.

3.2.4. EUnetHTA's approach to subgroups

Subgroup analyses are used in almost all assessments. However, EUnetHTA does not apply a standard set of mandatory subgroups. Applied subgroups mainly related to distinct research questions such as pretreatment and different lines of treatment (Ustekinumab; Pazopanib); age related AEs (Varicella – zoster Vaccine, Vorapaxar) or Body Mass Index (Sotagliflozin). Comprehensive subgroup analyses where e.g. conducted in the Hepatits C (Genotype and line of treatment). By contrast, in Ramucirumab no predefined subgroups analysis was conducted and in Midostaurin subgroup analyses were mostly used within the indirect comparisons.

3.2.5. EUnetHTA's value comments and outcomes of national appraisals

The results of the national appraisals in France, Germany, Italy and the UK as well as the concluding comments from EUnetHTA are shown in Fig. 2. Overall, a high heterogeneity of HTA appraisals across the four countries was observed. Only 3 procedures (Alectinib, Midostaurin, and Hepatitis C) received positive recommendations in all 4 countries. No G—BA appraisals were conducted for Regorafenib (medicine was withdrawn from the German market prior to the HCC indication) and Sorafenib (medicine was introduced prior to AMNOG). However, those products also received positive ratings at least in certain subgroups with the French, Italian and British HTA body. Vorapaxar was only appraised by the French HTA body before it was withdrawn from the market. Ramucirumab, Canagliflozin, the Varicella – zoster Vaccine, and Pazopanib received different appraisals across the countries.

Concluding EUnetHTA comments trended positive for Ustekinumab (non-biologic failure population), Alectinib, Midostaurin, Hepatitis C, and Ramucirumab and negative in Sotagliflozin. Both positive and negative conclusions were included in the assessments of Regorafenib, Vorapaxar, Sorafenib, Canagliflozin and in the Varicella – zoster Vaccine. The PFS benefit in Pazopanib was acknowledged, but clinical value was discussed controversially.

4. Discussion

Multiplicity is a well-known challenge in clinical trials. The underlying concern with multiplicity is that unsubstantiated claims may be made as a consequence of an inflated rate of conclusions [17]. Currently 81 European HTA bodies are acting under the EUnetHTA umbrella with some countries even contributing with more than one HTA body. Considering the multiple HTA bodies included in HTA assessments and appraisals across Europe and the resulting heterogeneity of HTA appraisals among the countries (see e.g. the national appraisals in Fig. 2), the *risk of multiplicity within the various national HTA procedures* becomes obvious. While it is a limitation of our comparison that we've only selected the four largest European markets it may be assumed that the heterogeneity prevails when including additional HTA bodies across Europe. The initiative by the EC to strengthen a joint European HTA assessment and leaving the authority for HTA appraisals within the countries therefore seems timely and urgently required.

So far EUnetHTA's pharmaceutical assessments are initiated on a voluntary basis and EUnetHTA's experience with REAs is limited. Since September 2012, when the first assessment on Pazopanib has been published only 12 procedures were finalized, with another 8 assessments in process. This represents only a fraction of the appraisals that key HTA bodies such as G-BA, HAS, or NICE are routinely publishing [18]. Furthermore, only in three procedures (Sotagliflozin, Hepatitis C products, Varicella – zoster Vaccine) EUnetHTA did cover the full licensed indication of the respective medicines. The limited and fragmented coverage of new and/or extended pharmaceutical marketing authorizations places an important obstacle towards a more standardized national implementation of EUnetHTA's assessments. Therefore, any further planning on EUnetHTA's evolving role beyond JA3 should definitely address the challenge of reaching a *more comprehensive coverage* in at least a specific disease area or type of condition (e.g. rare or ultrarare conditions).

Comparing the evolution of EUnetHTA's assessment across JA1, 2, and 3 reveals that process characteristics are steadily improving. Considerable improvement has been made for example since JA3 with regard to *timing of REAs*. While e.g. the assessment of Sorafenib was published 298 days after EMA approval the 5 available JA3 assessments where published within 80 days after EMA approval and well ahead of the national appraisals. In order to facilitate the impact of EUnetHTA's assessments on national appraisals, it seems best to target for a publication of the assessments at the time of or shortly after EMA approval. The timely publication of the most recent assessments on Ustekinumab and Sotagliflozin (49 and 42 days after EMA approval) should therefore be considered to be setting ambitious albeit realistic timelines.

All content considerations included in this review (appropriate evidence base; right comparator(s); endpoints; subgroups) are also part of the regulatory process that each new medicine/ new indication has to undergo. A *consolidated regulatory and HTA approach to available clinical evidence* therefore is a key opportunity when considering an evolving role of EUnetHTA in European HTA assessment. It is well-known that clinical, regulatory, and HTA decision making are leveraging different components of evidence-based medicine [13,14,19]. However, as regulatory and HTA bodies rely on the same set of clinical data further alignment of their mutual data needs and approaches seems critical to strengthen the European impact into global clinical development programmes [20]. Definition of clinical trial evidence requirements, suggested endpoints, appropriate comparative therapies, and pre-defined subgroups should ideally be advised jointly between EMA and EUnetHTA to ensure optimal use of resources within the industry. Considering for example the

fact that primary clinical trial endpoints that were agreed with ethics committees and EMA are considered to be not relevant to patients by the German HTA body G—BA is counter-intuitive [21]. The more pragmatic approach to clinical endpoints as can be seen in EUnetHTA's REAs of e.g. Alectinib and Sorafenib seems appropriate to address this challenge. The increasing number of joint EMA/ EUnetHTA advices preceding the REAs are an ideal approach to gradually develop a joint regulatory and HTA view on the clinical value of pharmaceutical development programmes. Required data to be included in EMA's 'Summary of Product Characteristics' and within the HTA reports should overlap to a large extent in order to provide a clear guidance to the researching industry.

While EUnetHTA does not yet have standardized procedures with regards to appropriate comparative therapies, required subgroup analyses or defined thresholds indicating additional benefit, this review of 12 REAs across JA 1,2, and 3 indicates that consistent content characteristics are evolving. Generally speaking, *EUnetHTA aims to take a rather inclusive view on available evidence.* The totality of available comparative clinical evidence rather than only the fragment of data e.g. derived from randomized clinical trials against a predefined comparator seem to determine EUnetHTA's considerations:

- Recent JA3 assessments include thorough reflections on appropriate comparative therapy: in Ustekinumab both, active and inactive (Placebo) comparators were included, in Sotagliflozin a NMA was leveraged including active comparators (Empagliflozin and Dapagliflozin), in Alectinib an indirect comparison vs a recently introduced comparator (Ceritinib) was leveraged and in Midostaurin EUnetHTA pointed to the lack of comparative treatments in FLT + patients.
- Omission of key components of evidence as e.g. routinely practiced by IQWIG and G-BA has not be seen with EUnetHTA. While e.g. IQWIG rejected 94 % of submitted indirect treatment comparisons [22,23] EUnetHTA included evidence derived from NMAs or ITCs in 7 out of the 11 their assessments. Despite prevailing concerns regarding uncertainty of indirect evidence, EUnetHTA does include them frequently in their final considerations. In Sotagliflozin EUnetHTA concluded that *'it is of note that neither dose of Sotagliflozin was ranked in first position for any of the outcomes included in the NMA'* [24] In the Alectinib REA the conclusion refers to uncertainty but suggests that: *'from an indirect comparison, an advantage of Alectinib versus Ceritinib is indicated for PFS'* [25]. In particular in an environment of increasing complexity, ever more targeted medicines and accelerating rates of medical innovation the acceptance of indirect evidence in EUnetHTA's assessments seems reasonable and also in line with the practice of e.g. NICE and HAS. Real World Evidence was not yet part of the reviewed 12 REAs.

5. Conclusion/ policy recommendation

In conclusion, a joint European HTA assessment is a first step to address the challenge of heterogeneity across the multiple national HTA bodies acting under the EUnetHTA umbrella. Availability of a European HTA assessment shortly after EMA approval might support acceleration of national appraisals within the European Union Member States [26]. Nevertheless, key components of the HTA process i.e. the evaluation of non-clinical domains (e.g. costs) and the final appraisal will remain at national level, allowing for a stepwise implementation of a consolidated European Perspective on Comparative Effectiveness and Safety.

Declaration of Competing Interest

r-connect ltd received financial support from F. Hoffmann-La Roche for running the analysis and medical writing services.

References

[1] Jain M, Nallagangula TK, Jawla S, Rai N, Dev D, Weber S, et al. Heterogeneity in relative efficacy assessments (REA) across european HTA bodies: opportunity for improving efficiency and speed of access to patients? Value Health 2015;18:A520.
[2] https://www.eunethta.eu/rapid-reas/8 (accessed Jan 3rd, 2020).
[3] https://www.eunethta.eu/services/early-dialogues/8 (accessed Jan 3rd, 2020).
[4] Giuliani G, Chassagnol F, Traub D, Gyldmark M, Hebborn A, Ducournau P, et al. Leveraging EUnetHTA's conceptual framework to compare decision drivers in France, Italy, and Germany from a manufacturer's point of view. Health Econ Rev 2018, http://dx.doi.org/10.1186/s13561-018-0201-y.
[5] Gyldmark M, Lampe K, Ruof J, Pöhlmann J, Hebborn A, Kristensen FB. Is the EUnetHTA Core® Model fit for purpose? Evaluation from an Industry Perspective. Int J Technol Assess Health Care 2018;34:458–63.
[6] Ampelas AE, Schmitz J. Strengthening EU cooperation on health technology assessment. Interdisciplinary platform on benefit assessment. European benefit assessment – opportunities and risks, 8; 2019. p. 8–13.
[7] Haute Autorité de Santé. https://www.has-sante.fr (accessed Jan 3rd, 2020).
[8] Gemeinsamer Bundesausschuss. https://www.g-ba.de (accessed Jan 3rd, 2020).
[9] Agenzia Italiana del Farmaco. http://www.agenziafarmaco.gov.it (accessed Jan 3rd, 2020).
[10] National Institute for Health and Care Excellence. https://www.nice.org.uk/about/who-we-are (accessed Jan 3rd, 2020).
[11] Tafuri G. A Glance into EUnetHTA's perspective on evidence requirements. Interdiscip Platform on Benefit Assess 2019;9:58–61.
[12] European Commission. Proposal for a Regulation of the European Parliament and of the Council on Health Technology Assessment and Amending Directive 2011/24/EU. https://ec.europa.eu/health/sites/health/files/technology_assessment/docs/com2018_51_en.pdf (accessed Jan 3rd, 2020).
[13] Tafuri G, Pagnini M, Moseley J, Massari M, Petavy F, Behring A, et al. How aligned are the perspectives of EU regulators and HTA bodies? A comparative analysis of regulatory-HTA parallel scientific advice. Br J Clin Pharmacol 2016;82:965–73.
[14] Motola D, De PF, Poluzzi E, Martini N, Rossi P, Silvani MC, et al. An update on the first decade of the European centralized procedure: how many innovative drugs? Br J Clin Pharmacol 2006;62:610–6.
[15] Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997;50:683–91.
[16] Meremetidis A, Ferrario M, Giuliani G. The new AIFA innovation framework to recognize innovative drugs: a preliminary analysis of key decision drivers of evaluation. Value Health 2018;21(Suppl. 3):160.
[17] Committee for Proprietary Medicinal Products (CPMP). Points to consider on Multiplicity issues in Clinical Trials. CPMP/EWP/908/99. https://www.ema.europa.eu/en/documents/scientific-guideline/points-consider-multiplicity-issues-clinical-trials_en.pdf (accessed Jan 3rd, 2020).
[18] Ruof J, Schwartz FW, Schulenburg JM, Dintsios CM. Early benefit assessment (EBA) in Germany: analysing decisions 18 months after introducing the new AMNOG legislation. Eur J Health Econ 2014;15:577–89.
[19] Schlegl E, Ducournau P, Ruof J. Different weights of the evidence-based medicine triad in regulatory, health technology assessment, and clinical decision makin. Pharm Med 2017;31:213–6.
[20] Wang T, McAuslange N, Liberti L, Leufkens H, Hövels A. Building synergy between regulatory and HTA agencies beyond processes and procedures – can we effectively align the evidentiary requirements? A survey of stakeholder perceptions. Value Health 2018;21:707–14.
[21] Ruof J, Flückiger O, Andre N. Early benefit assessment in oncology in Germany: how can a clinically relevant endpoint not be relevant to patients. Drugs R D 2015;15:221–6.
[22] Lebioda A, Gasche D, Dippel FW, Theobald K, Plantör S. Relevance of indirect comparisons in the German early benefit assessment and in comparison to HTA processes in England, France and Scotland. Health Econ Rev 2014;4(31).
[23] Werner S, Lechterbeck L, Rasch A, Merkesdal S, Ruof J. Analysis of acceptance rate and rationales for rejection of indirect comparisons in IQWIG's benefit assessments. Ges. Ökon. Qual. Management 2019; 2019, http://dx.doi.org/10.1055/a-0890-7985.
[24] EUnetHTA. Assessment on Sotagliflozin. https://www.eunethta.eu/wp-content/uploads/2019/06/PTJA04-Final-Assessment-Report-V1.pdf (accessed Jan 3rd, 2020).
[25] EUnetHTA. Assessment on Alectinib. https://www.eunethta.eu/wp-content/uploads/2018/01/PTJA03_Alectinib_Final_Assessment_Report-revised_version_Feb_2018.pdf (accessed Jan 3rd, 2020).
[26] Woelken T. A modern approach to Health Technology Assessment https://www.theparliamentmagazine.eu/articles/opinion/modern-approach-health-technology-assessment (accessed Jan 3rd, 2020).
[27] Schünemann HJ, Best D, Vist G, Oxman AD. Letters, numbers, symbols, and words: howe best to communicate grades of evidence and recommendations? CMAJ 2003;169:677–80.