RE-SUBMISSIONS WITH RWE: CAN THEY HELP CHANGE YOUR BENEFIT RATING?

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INTRODUCTION

In recent years, there has been increased interest in utilizing real-world evidence (RWE) to demonstrate a therapy's benefit outside of a controlled clinical trial setting. Innovative treatments are often launched with a lack of robust supporting data in order to expedite patient access. However, this leads to payer uncertainty during health technology assessments (HTA) and can often be detrimental to the outcome of the product's HTA. This is especially true in France and Germany due to the rigidity of their assessment procedures and focus on clinical data methodology. Following a negative HTA decision, manufacturers often submit additional data for re-assessment of their product. Re-assessments based on real-world post-marketing data are becoming increasingly common across global markets; however, the magnitude of impact from RWE in influencing HTA outcomes is not yet defined.

OBJECTIVE

Our research aims to understand the role of RWE in re-submissions and determine if this type of evidence can help to improve HTA outcomes when products are re-assessed by the Haute Autorité de Santé (HAS) in France and Gemeinsamer Bundesausschuss (G-BA) in Germany.

METHODOLOGY

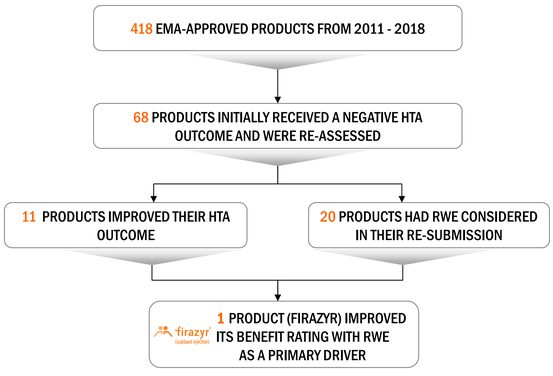
Therapies approved by the European Medicines Agency (EMA) from 2011 - 2018 were compiled (N=418, Figure 1) followed by analyses to identify products that initially had a negative HTA outcome (defined as ASMR IV or V in France and "no additional benefit" in Germany) and were re-assessed. Subsequently, initial and re-assessment HTA documents were evaluated in order to discover the number of drugs that decreased, maintained, or improved their HTA outcome, and the number that included RWE in their re-submission. Pharmaceutical therapies indicated for chronic conditions, in addition to oncology therapies, were prioritized for further analysis. Finally, for those products that included RWE, commentary on the submitted evidence from HTA bodies vs. the EMA was analyzed to understand the role of RWE in the re-submission and how it affected the product's benefit rating.

RESULTS

KEY NUMERICAL RESULTS:

N=51 and N=17 drugs were identified as having been re-assessed in France and Germany respectively. RWE was considered in N=19 (37.3%) products' re-assessments in France, but only N=1 (5.9%) in Germany. In France N=7 (13.7%) products improved their ASMR score (N=3 from ASMR V to ASMR IV and N=4 from ASMR IV to ASMR III), with N=1 of these benefit rating increases driven by RWE, as shown in Figure 2. In Germany N=4 (23.5%) products improved their additional benefit rating (N=1 to "minor additional benefit" and N=3 to "considerable additional benefit"), with N=1 of these submitting RWE as part of the re-assessment, although this evidence was not analyzed by the G-BA as part of the decision.

FIGURE 1: FILTER METHODOLOGY



Source: CBPartners Secondary Research; EMA: European Medicines Agency; HTA: Health technology assessment; RWE: Real world evidence; ASMR: Amélioration du Service Médical Rendu

ROLE OF RWE IN REASSESSMENT DECISION-MAKING

In Germany, RWE was not the major driver of an improved benefit rating for any analyzed product. In France, N=1 product, FIRAZYR, improved its HTA outcome based on RWE. FIRAZYR is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults. It was initially assessed in July 2008 and given an ASMR IV primarily based on the statistically significant primary endpoint in the FAST-2 Phase III randomized controlled trial (RCT). Given the urgent nature of HAE attacks, the HAS recommended making FIRAZYR available in a form that could be self-administered by patients. Ten years later in July 2018, the HAS initiated re-assessment of FIRAZYR alongside competitors (BERINERT, CINRYZE, and RUCONEST) to streamline the list of billable medicines indicated for HAE. The manufacturer submitted a post-hoc analysis of the Phase III FAST-3 clinical trial, in addition to RWE in the form of five retrospective observational studies from the international Icatibant Outcome Survey (IOS) register to validate results shown in RCTs and demonstrate self-administration in real-world practice. This data addressed the HAS' concerns surrounding self-administration and was noted as the primary driver of an improved ASMR III rating. This case study shows that long-term RWE through patient registries can alleviate initial product uncertainty and drive an improved benefit rating. However, given only N=1 example was found, it is rare that RWE is a primary decision driver during re-assessments.

Other forms of evidence are often given more weight during a product's re-assessment. For example, ELIQUIS initially received an ASMR V in France due to issues with the indirect comparison methodology and concerns with appropriateness of the RCT patient population. Subsequently the HAS initiated reimbursement renewal assessment of new oral anticoagulants and ELIQUIS was able to improve its ASMR rating to IV based on post-hoc RCT analysis and indirect meta-analyses; no RWE was submitted. The HAS did flag the lack of RWE as a weakness in the initial assessment and highlighted that no RWE was submitted for the re-assessment. However, the lack of RWE was outweighed by other forms of evidence that warranted an increase in ASMR score, highlighting that RWE may not be a key driver in France's HTA decisions. These findings emphasize that RCT data is the gold standard from an HTA perspective in France and Germany and alternative forms of evidence, such as meta-analysis are equally sufficient as RWE at supporting a products' demonstrated benefit.

We undertook analysis of re-assessment benefit rating outcomes across Germany and France by therapeutic area (Figure 3) to understand if there are specific indications for which RWE is most beneficial. The analysis shows that oncology products are often re-assessed, with improved benefit ratings occasionally obtained. These enhanced HTA outcomes, however, were mostly driven by final analysis of pivotal Phase III RCTs, which is not surprising given that many oncology therapies launch into areas of high unmet need with incomplete data packages.

STRICT METHODOLOGICAL REQUIREMENTS EXIST FOR RWE

While RWE can be valuable during HTA re-assessments, as demonstrated by FIRAZYR, multiple examples show how HTA bodies only consider those studies that are methodologically sound and have undergone final analysis. In France, JEVTANA initially received an ASMR IV in October 2011 based on demonstrating an overall survival benefit in the pivotal Phase III TROPIC study. For JEVTANA's re-assessment in October 2012, the manufacturer submitted ATU tolerance data, intermediate results from three ongoing observational studies on the safety of JEVTANA in real-world conditions and subgroup analysis results from the TROPIC study. The HAS stated that the ongoing observation studies did "not allow any conclusions to be drawn" given that no study reports or final analyses were available. Similarly, ATU data did not provide any definitive conclusions given an absence of information on the number of treatment cycles received and limited serious-adverse event data. Therefore, the primary drivers behind JEVTANA's increased ASMR rating were final results and sub-group analysis of the pivotal TROPIC study in addition to the shifting prostate cancer treatment landscape (the HAS considered JEVTANA an alternative to ZYTIGA, a competitor that received an ASMR III for the same indication). Similarly, AFINITOR initially received an ASMR V in France, however the product was able to improve this to an ASMR IV upon re-assessment due to new clinical data from the final analysis of the BOLERO-2 phase III study. Tolerance data from an interim analysis of an observational study in Germany (BRAWO) was also submitted; however, the HAS did not accept this because the data was only available in abstract form and the complete clinical report was not yet available. These case studies highlight that while RWE can be used to supplement clinical trial findings, it is important to submit complete RWE data to provide HTA bodies with certainty on a product's effectiveness in the real-world.

In-addition to complete studies, long-term RWE is highly valued by HTA bodies. In 2014 OPSUMIT received an ASMR V in France given that its RCT (SERAPHIN) was placebo controlled and a direct comparison would have been possible in the pulmonary arterial hypertension (PAH) space. The manufacturer re-submitted to the HAS in 2015, including RWE in the form of the OPUS9 US-based patient registry and used the REVEAL registry to model one indirect comparison. However, there was no change in OPSUMIT's ASMR score. The HAS commented on the lack of long-term data available from the interim RWE analysis, suggesting that waiting until RWE data are more robust before resubmitting may result in a more positive perception. In comparison to the one year of RWE gathered in the OPSUMIT and JEVTANA examples, FIRAZYR's improved benefit rating was obtained 10 years after the HAS' initial assessment. This shows that while RWE is often appreciated by the HAS, longer-term data may be more impactful during a re-submission.

RWE SUPPORTS A COMPREHENSIVE PRODUCT DATASET

Often when initially assessing a product, HTA bodies such as the HAS will ask for a manufacturer to conduct subsequent studies to confirm preliminary results. Undertaking real-world studies and gathering RWE is an effective and efficient way of collecting this data to mitigate concerns. GILENYA was assessed in 2011 in France for treatment of relapsing remitting multiple sclerosis (RRMS). The product initially received an ASMR IV in France with the HAS noting the lack of long-term safety data and requesting that the manufacturer implement an RWE observational study to better understand the product's clinical impact. In 2018, the HAS initiated reimbursement renewal assessment of drugs indicated for highly active MS. The manufacturer submitted a long-term RCT follow-up study and 8 observational studies including the VIRGILE observational study. This long-term data and RWE fulfilled the assessment request by mitigating initial safety concerns and allowed GILENYA to maintain its ASMR IV rating. This example demonstrates that RWE can be a strong supportive aspect of a product's dataset, helping to offset uncertainty in the case of a class review.

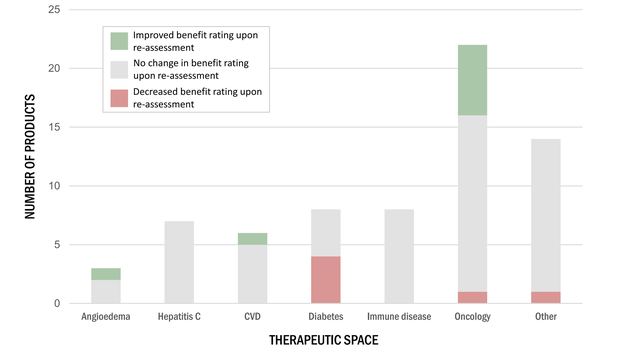
RWE PERCEPTION NUANCES BETWEEN FRANCE & GERMANY

Through this analysis it is clear that fewer re-assessments were undertaken in Germany (N=17 in Germany vs. N=51 in France) and less RWE was considered during these re-assessments (N=1 in Germany vs. N=19 in France, Figure 2). We have demonstrated above that the HAS will consider RWE during HTA assessments; however, there is less evidence that the G-BA will act similarly. For example, GILENYA was initially assessed in Germany in 2012 receiving a "minor additional benefit" for one subgroup and "no additional benefit" in two subgroups. In 2015 the manufacturer subsequently initiated re-assessment in Germany submitting multiple forms of data such as a long-term RCT follow-up study and the PANGAEA Germany-specific RWE study. While GILENYA was able to improve from "no additional benefit" to "considerable additional benefit" in one subgroup, the G-BA did not comment on the RWE during the benefit assessment, suggesting that RWE is less of a driver in this market. In this example, re-assessment had significant pricing implications for GILENYA, as with its improved benefit rating it was able to obtain a higher price in Germany (8% price increase from 2015-2017) vs. competitors that received a "no additional benefit" rating (TECFIDERA saw a 30% price decrease from 2015-2016). Overall, France appears more open to RWE compared to Germany which does not typically comment on RWE in the benefit assessment. However, this stance towards RWE may be changing in Germany given recent draft legislation[3] that allows the G-BA to mandate the collection of observational RWE as a condition of the reimbursement of orphan products. Legislation changes such as this indicate that RWE is becoming increasingly accepted across markets; however, currently it is not a primary driver behind HTA re-assessments.

FIGURE 2: RE-ASSESSMENT BENEFIT RATING OUTCOMES BY GEOGRAPHY

Source: CBPartners Secondary Research

FIGURE 3: RE-ASSESSMENT BENEFIT RATING OUTCOMES BY THERAPEUTIC SPACE



Source: CBPartners Secondary Research; CVD: Cardiovascular disease; Note: Other includes blood clots, duchenne muscular dystrophy, epilepsy, eye disease, lung disease, skin disease and urological conditions

KEY TAKE-AWAYS

- Ensure the design of observational studies are methodologically sound with regards to variables such as the patient population by following relevant guidelines
- Consider the timing of resubmission as longer-term final data is most impactful and interim results may not be accepted
- Establish a balanced data package comprised of RCT data supported by RWE and additional analysis
- Consider the target geography, their approach towards RWE and how perceptions may change in the future

CONCLUSION

This research highlights that HTA re-assessments are a useful tool to increase a product's pricing and market access opportunities across markets; however, the evidence package for re-submission must be carefully considered. Please see our key takeaways when utilizing RWE during a re-submission. To conclude, RWE alone is unlikely to improve HTA outcomes, but RWE that supports clinical trials by confirming a long-term benefit could be valuable for re-submissions.

REFERENCES: [1] CBPartners, London, UK; [2] CBPartners, New York, NY, USA; [3] Gesetz für mehr Sicherheit in der Arzneimittelversorgung (GSAV), Drucksache 19/8753 (27th March 2019)