Retrospective analysis of the French early access experience following the 2021 reform

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Background and objective

- Since reform was implemented in July 2021, EA in France has been granted for drugs meeting all of the following criteria (1):
  1. Severe, rare, or debilitating disease
  2. Lack of appropriate treatment
  3. Impossibility to defer treatment initiation
  4. Presumed positive risk-benefit ratio
  5. Presumptively innovative nature
- After a favourable opinion on the risk-benefit assessment from ANSM, products are then assessed by the HAS. The TC issues an opinion and HAS provides the final decision
- This study aimed to analyse the French EA experience since the reform

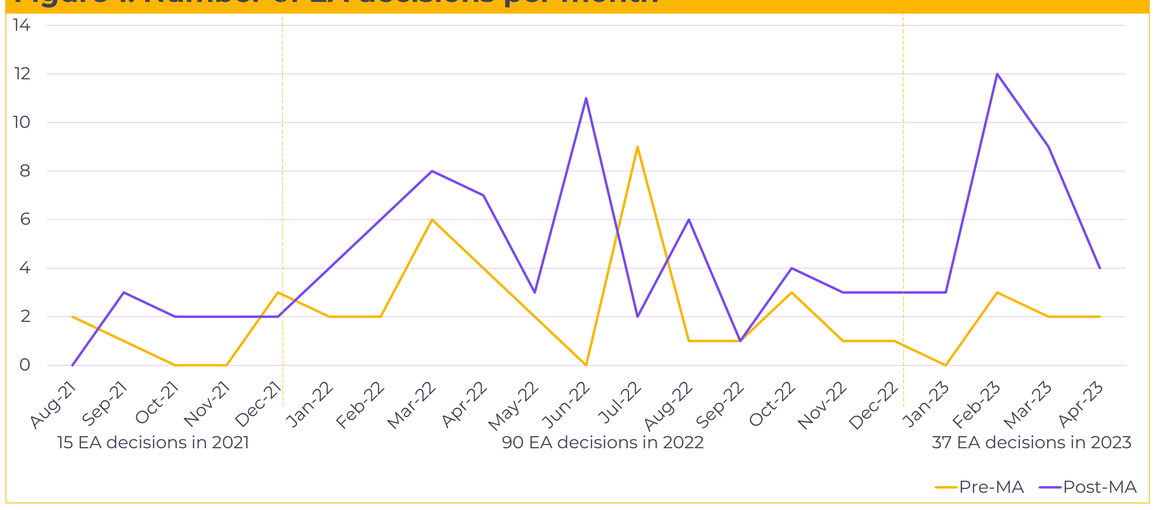
Methods

- All EA decision reports published by the HAS between 1 July 2021 and 30 April 2023 were identified and analysed (2)
- Extracted information included the following:
  - Product characteristics (MA date if available, orphan drug status, therapeutic area)
  - EA request characteristics (new request, renewal, publication date, submission date)
  - Assessment of eligibility criteria
  - Submitted clinical data
  - EA decisions based on the ANSM, HAS TC, and HAS college conclusions

Results

- Before April 2023, 142 EA decisions related to 90 drugs were identified, with up to 90 EA decisions over 1 full year (2022) (Figure 1)
  - Forty-six products had more than 1 EA request for different indications or were reassessed within the EA program)
- Most EA decisions were post-MA (68%) (Figure 2)
- One hundred and twenty decisions (85%) were positive; 22 (15%) were negative (Figure 3)
- Among the positive EA decisions, 37.5% of drugs had an orphan drug designation

Figure 1. Number of EA decisions per month[a]



[a]Based on the HAS college decision date

Figure 2. Distribution of pre- and post-MA requests

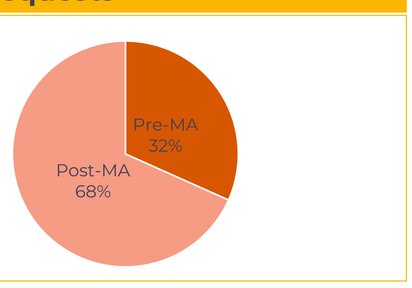
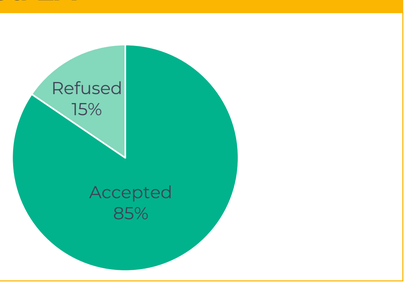
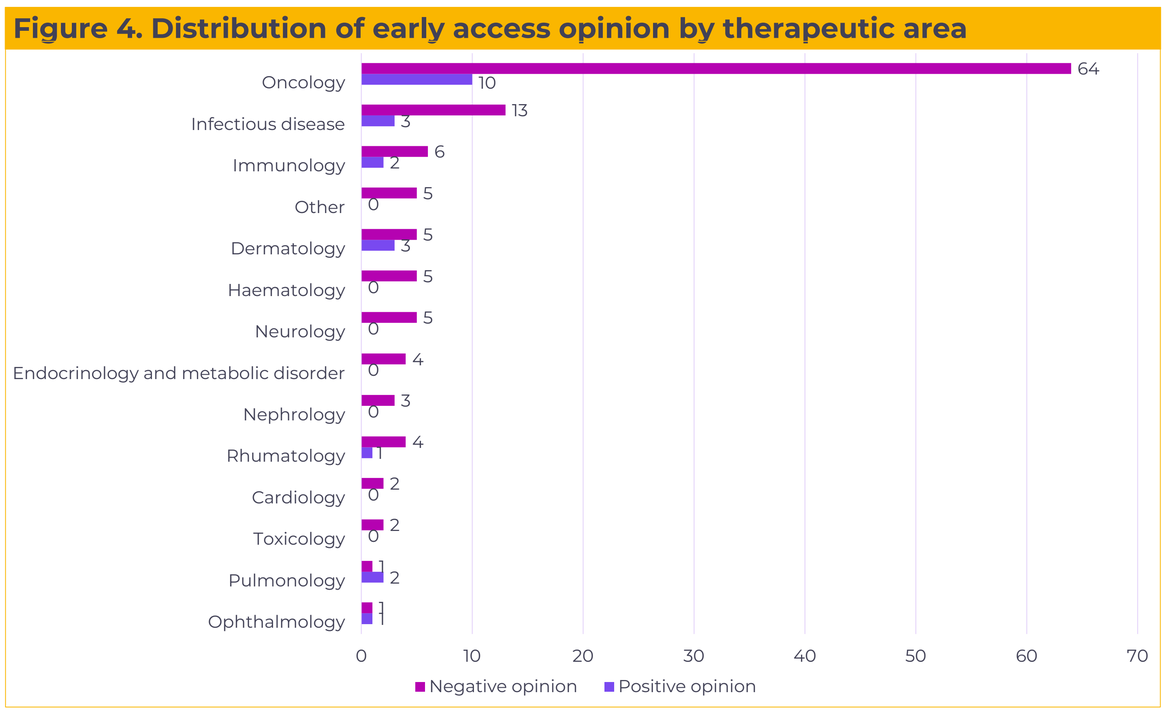


Figure 3. Distribution of accepted and refused EA



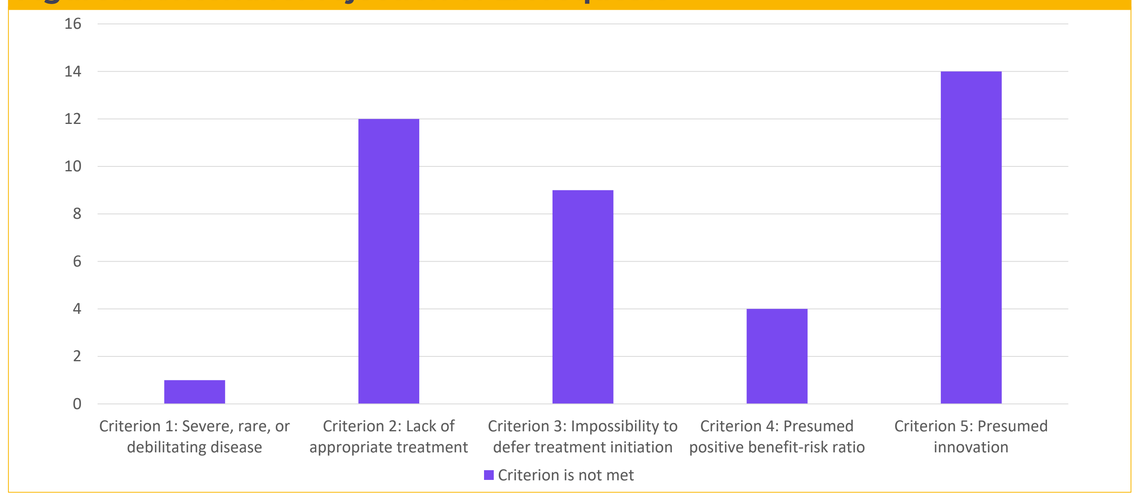
- A few products (making up 5% of positive EA requests) had a restricted indication:
  - One drug had its indication restricted by ANSM due to a lack of risk-benefit demonstration in the excluded subpopulation
  - Six drugs had their indications restricted by HAS based on the following criteria (with some overlap): severe, rare, or debilitating disease (3 drugs); lack of appropriate treatment (3 drugs); impossibility of deferring treatment initiation (4 drugs); presumptively innovative nature (3 drugs)
- The HAS college followed 94% of TC recommendations for EA. In 7 cases, it granted an EA despite negative TC recommendations. Once, it issued a negative decision despite a positive TC recommendation
- The average process duration from request submission to HAS decision for a pre-MA EA drug was 89 days (90 days specified in the regulation). This was shorter for post-MA EA requests (78 days), probably as post-MA requests are not reviewed by ANSM
- The major therapeutic area of the EA applications was oncology (64 positive opinions and 10 negative opinions), followed distantly by infectious disease (13 positive opinions and 3 negative opinions) (Figure 4)

Figure 4. Distribution of early access opinion by therapeutic area



- The lack of demonstration of a positive risk-benefit ratio, as appraised by the ANSM, led to the systematic rejection of 4 EA requests (18%) without HAS assessment (Figure 5)
- Fourteen EA rejections (63%) resulted from non-validation of the presumed innovation criterion, 12 (54%) from the availability of an appropriate treatment, and 9 (41%) from the possibility of deferring treatment (Figure 5)

Figure 5. Criteria for rejection of EA requests



Discussion

- Since the EA reform in France, most EA requests have been accepted
- However, approximately 15% of cases are rejected. When excluding rejections due to the lack of presumed risk-benefit ratio by the ANSM, the main criteria for rejection were lack of appropriate treatment, impossibility to defer treatment initiation, and presumed innovation
- The lack of an appropriate treatment (criterion 2) is a key criterion that must be justified by assessing the current limitations of therapeutic alternatives used in French clinical practice
  - An appropriate treatment is different from a clinically relevant comparator, as defined by the TC for reimbursement decisions. HAS considers an appropriate treatment to be a clinically relevant comparator, although the inverse is not true
  - To be considered an appropriate treatment, the new therapeutic alternative needs to be presumed to have a better efficacy and/or better safety/tolerability profile; to improve patients' quality of life; to have a positive impact on the healthcare organisation; to improve the goal of treatment (from palliative to curative); or to provide a new pharmaceutical formulation adapted to a specific population, like children
  - The presumed innovation criterion (criterion 5) is based on the appropriateness of the clinical development plan, considering the current therapeutic strategy, but also encompassing additional conditions that incorporate other criteria, such as the presumed benefit in the therapeutic strategy and how it may address unmet medical needs
- It is also important to point out that the HAS and ANSM may identify subpopulations of the claimed indication that may lead to EA restrictions
- At the time of writing, HAS had published an overview of EA decisions with a cut-off date for EA decisions of 30 June 2023; even if the actual figures differed slightly due to cut-off date differences, we identified similar trends (3)

Conclusions

- With the 2021 EA reform in France, HAS demonstrated a strong wish to promptly issue decisions on EA requests, allowing access to several presumably effective and innovative drugs—especially in oncology—to patients suffering from high unmet medical needs
- However, a small proportion of EA requests continue to be rejected. In addition, in a few cases, the indication was restricted or the final HAS college decision was not systematically aligned with TC recommendations. Further research is needed to assess the potential impact of such rejections on final reimbursement decisions
- Engaging in EA will require clear strategic positioning and an understanding of the potential place of the drug in the French therapeutic strategy. This will include the assessment of potential subpopulations expected to benefit most from EA, along with a robust rationale and compelling argument to appropriately address the different and sometimes overlapping EA criteria

Abbreviations: ANSM, Agence Nationale de Sécurité du Médicament et des Produits de Santé; EA, early access; HAS, Haute Autorité de Santé; MA, marketing authorisation; TC, transparency committee

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