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Coverage and pricing recommendations of the French National Health Authority for innovative drugs: a retrospective analysis from 2014 to 2020

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Keywords

Health Technology Assessment; reimbursement; drug pricing; clinical benefit; clinical added value; economic evaluation; incremental cost-utility ratio; France

Running Title

Determinants of innovative drugs' value in France

Summary

This study provides a retrospective analysis of the recommendations of the French National Health Authority on the reimbursement and pricing of innovative drugs.

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Coverage and pricing recommendations of the French National Health Authority for innovative drugs: a retrospective analysis from 2014 to 2020

Highlights

- The analysis of the recommendations of the French National Health Authority for innovative drugs entering the market between 2014 et 2020 shows that not all official criteria are considered in the reimbursement and pricing decisions which questions the transparency and predictability of the French HTA process.
- Although the clinical and economic assessments are independent in the French HTA process, results show consistency between the clinical and economic evaluations regarding the added value of new drugs.
- We document the ICUR levels of innovative drugs in France and we find that drug and disease characteristics associated with the ICURs vary across the ICUR distribution.

Abstract

Objective

This study provides a retrospective analysis of the recommendations of the French National Health Authority on the reimbursement and pricing of innovative drugs.

Methods

The analysis includes drugs subjected to both economic and clinical evaluations in France from 2014 to 2020. Ordered logistic and quantile regressions are used to estimate the factors associated with the clinical value (SMR), the clinical added value (ASMR) and the Incremental Cost-Utility Ratio (ICUR) of innovative drugs. All variables used in the regression analyses are extracted from the Clinical and Economic Opinions for the 146 observations.

Results

Regression analyses indicate that two out of the five official criteria, the efficacy-adverse events balance of the drug and its function, are significantly associated with the SMR rating. The ASMR is positively associated with the disease severity, the QALY gain provided by the drug and the validation of the ICUR in the Economic Opinion. At the first quartile of the ICUR distribution (around 50000€/QALY), higher ICUR levels are observed for drugs with a smaller target population and for drugs claimed as more innovative. Higher ICUR levels are also observed for pediatric drugs and for drugs with no therapeutic alternative at the third quartile of the distribution (around 240000€/QALY).

Conclusion

Not all official criteria of the SMR are associated with actual ratings obtained. Regarding the ASMR, the results support the idea of a convergence between the two independent clinical and economic appraisal processes. Finally, the factors influencing the ICUR level vary across the distribution of ICUR.

1. Introduction

Health Technology Assessment (HTA) is used to inform decision making on health technologies' reimbursement and pricing in most developed countries and as such critically contributes to the access of patients to safe and effective innovative drugs while maintaining the financial sustainability of socialized health systems. At the European Union (EU) level, while market authorizations are centrally issued by the European Medicines Agency, HTA remains the prerogative of decentralized national HTA bodies which has contributed to delays and inequalities in availabilities of innovative health technologies for patients [1].

In France, the HTA process for innovative drugs includes both clinical and economic evidence assessments conducted independently and simultaneously by two commissions of the French National Health Authority (HAS), respectively the Transparency Commission (CT) and the Economic and Public Health Evaluation Commission (CEESP).

The assessment of the clinical value of new drugs relies on two main composite indicators, namely the SMR and the ASMR. The SMR rates the drug's clinical benefit on a four-level scale from 'insufficient' to 'important' and drives the reimbursement rate granted by the national health insurance. The ASMR rates the clinical added value of the drug on a five-level scale, from 'no therapeutic progress' to 'major therapeutic progress' and conditions the price level that the manufacturer can claim in its negotiation with the Committee of Health Product (CEPS). The Clinical Opinion issued by the CT decides on the SMR and ASMR obtained by new drugs. The determination of the SMR is based on five official criteria: 1) the severity of the disease; 2) the efficacy-adverse events balance of the drug; 3) the drug function; 4) its place in the therapeutic strategy and 5) its public health impact [2]. For the ASMR, even though official criteria are not clearly established by regulations as for the SMR, the CT doctrine recently clarified the dimensions considered in the rating process, i.e., the treatment effect size, the quality of the evidence and of the demonstration, and the medical need and severity of the disease [3].

Economic evaluation was first introduced in 2013 in the French HTA process and only concerns a subset of all drugs seeking reimbursement by the national health insurance. Indeed, the submission of cost-effectiveness evidence is mandated only for drugs claimed as innovative by their manufacturer at the time of the application for reimbursement, i.e., drugs with a claimed ASMR from 'moderate' to 'major' before the evaluation of the ASMR by the CT [4;5]. The CEESP reviews the reliability and the consistency of the economic evidence provided by the pharmaceutical firm. The Economic Opinion concludes on the validity of the QALY gain and of the ICUR level reported by the pharmaceutical firm and characterizes the uncertainty around this claimed ICUR [6]. This

information is used together with the ASMR to define the framework for price negotiation with the CEPS. However, in the absence of an official 'acceptable threshold' for ICURs in France, Economic Opinions are not binding for coverage and pricing decisions except in cases where the CEESP invalidates the reported ICUR and concludes that the efficiency of the drug is not demonstrated. In the latter case, the European price guarantee no longer holds.

The aim of this paper is to study the French upgraded HTA process following the introduction of economic evaluation in 2013. As economic evaluation is mandated only for drugs claimed as innovative by their manufacturers, the analysis is conducted on this subset of innovative drugs with two main objectives. The first objective is to investigate the factors associated with the SMR and the ASMR obtained by innovative drugs in France. Previous academic and institutional studies have highlighted several limitations of the SMR and ASMR rating process linked to a lack of clarity, a low discriminating power and an overlap of the criteria used in the assessment [7,8]. Within this first objective, we then more specifically aim to study the extent to which the official criteria and dimensions on which the SMR and ASMR must be based actually explain the SMR and ASMR obtained by innovative drugs after the CT evaluation. The second objective of the paper is to document the ICURs of innovative drugs which entered the French drug market between 2014 and 2020 as few studies have analyzed the influence of economic evaluation on HTA outcomes in France given its recent introduction in the assessment process. Filling this gap is of particular interest because there is limited information on the ICURs commonly accepted in France. More specifically, this study provides results on the characteristics of the drugs - in terms of disease severity, size of the target population, therapeutic innovation - that are associated with the ICURs claimed by pharmaceutical firms.

Within a growing literature on the revealed preferences of decisions makers for HTA criteria [9-12], our study is the first to provide a retrospective analysis of the recommendations made by the French HTA body including both clinical and economic evidence assessments. By documenting the clinical criteria actually considered in the reimbursement and pricing of innovative drugs in France, our study also provides information that will be useful for the forthcoming harmonization process of drugs' clinical evaluations among EU member states.

2. Data and methods

The analysis includes all drugs that applied for reimbursement between 2014 and 2020, with claimed ASMR from 'major' to 'moderate', apart from the six direct-acting antivirals (DAAs) against hepatitis C. The latter are excluded due to too many ICURs being presented for the different fibrosis statuses or genotypes (105 ICURs in 6 Economic Opinions on the 6 DAAs) which would lead to an over-representation of these drugs in the database and could bias the regression results. The specific case of DAAs should then be treated separately as was already done in a qualitative way for France in a previous study [13]. The drugs included are subjected to both clinical and economic evaluations by the CT and the CEESP as part of the regulatory HTA procedure. A total of 91 Economic Opinions, and their associated Clinical Opinions, are considered. Table A1 in Appendix A provides the list of all the Clinical and Economic Opinions studied, that are publicly available on the HAS website.

As some drugs applied for market authorizations for different indications during the study period, the 91 available Economic Opinions concern 68 different drugs. In the Economic Opinions, cost-effectiveness can be assessed for several sub-populations, leading to the calculation of several ICURs. These ICURs represent separate observations in the database. Then, the total number of observations in the database amounts to 146.

All variables used in the regression analyses are extracted from the Clinical and Economic Opinions. Table B1 in Appendix B provides a full description of the extracted data, their source and coding. The following development presents and justifies the independent variables used in the regression analyses.

For the regression analysis on the obtained SMR, the independent variables correspond to the five official SMR criteria. Based on the categories reported in the Clinical Opinions, the severity of the disease is dichotomized as 'life-threatening' or not. For the efficacy-adverse events balance of the drug, the seven categories reported in the Clinical Opinions are merged in three main categories: 'Not or poorly established, insufficient or low', 'Intermediate' and 'Important'. Given that few drugs have at least some public health impact (reported as 'likely', 'small' or 'moderate' in the Clinical Opinions), the public health impact is binary coded as 'yes' or 'no'. The coding of the drug function is based on the categories reported in the Clinical Opinions, i.e., 'Curative', 'Preventive' and 'Symptomatic'. The place of the drug in the therapeutic strategy is evaluated in our analysis by the existence of therapeutic alternatives which is reported as 'yes' or 'no' in the Clinical Opinions.

The latest activity report of the CT, in accordance with its doctrine, presents the three dimensions considered in the determination of the ASMR [14]: the quality of the evidence and of the demonstration, the treatment effect size, and the medical need. The objective of the regression analysis on the ASMR is to find out whether these

dimensions are significantly associated with the ASMR obtained by innovative drugs. All the variables chosen to embody these dimensions are extracted from the Clinical and Economic Opinions.

As the efficacy of almost all drugs is evaluated using comparative double blinded phase 3 RCTs, the quality of evidence and of the demonstration is operationalized through two variables: the primary endpoint reported in the efficacy study and the validation of the firm's reported ICUR by the CEESP in the Economic Opinion. The primary endpoint is clearly mentioned as an indicator of the demonstration's quality in the CT doctrine. The classification of the primary endpoints reported in the Clinical Opinions is made with a focus on the therapeutic area of oncology, given the high prevalence of cancer drugs in our sample (68 out of 146 observations) and the debate over the use of surrogate endpoints in cancer drugs' clinical efficacy studies [15-19]. The first two categories of the 'primary endpoint' variable allow to differentiate between final patient relevant and surrogate endpoints for cancer drugs while the third category gathers endpoints of drugs non-related to this therapeutic area. The three categories retained for the 'primary endpoint' variable are then: 1) overall survival in cancer drugs; 2) surrogate endpoints in cancer drugs; and 3) other primary endpoints. The Economic Opinion also documents the quality of the evidence and of the demonstration to the extent that the ICUR claimed by the firm may be invalidated if there is a major caveat regarding an aspect of the methodology used. Therefore, the ICUR validation by the CEESP is used as a proxy for the quality of the demonstration in the regression analysis of the ASMR. The second dimension, the treatment effect size, is defined in the CT doctrine as the magnitude of the effect of the drug relative to its comparator. The QALY gain reported in the Economic Opinion is used as a proxy for the treatment effect size in the regression analysis on the ASMR. Finally, the medical need is operationalized in the ASMR regression through two variables: the severity of the disease and the existence of therapeutic alternatives.

For the regression analysis on the claimed ICUR, the independent variables include drugs and diseases' characteristics commonly used in the literature to explain HTA agencies' coverage and reimbursement decisions [20-26]: the function of the drug, the existence of therapeutic alternatives, the severity of disease, the pediatric use of the drug and the size of the target population. To test whether reported ICURs are higher for drugs claimed as more innovative by pharmaceutical firms, the claimed ASMR is also used as an independent variable in this regression.

Table B2 in Appendix B provides full details regarding the matching between the official SMR criteria, the CT doctrine's ASMR dimensions and the variables used in the regression analyses.

The factors associated with the obtained SMR and ASMR are studied using ordered logit regressions which are appropriate for ordinate categorical variables with more than two categories. Given the wide variance in ICURs, quantile regressions are used to study the factors associated with the claimed ICURs. Quantile regressions, contrary to OLS regressions, allow to discriminate between the characteristics associated with the ICUR level along the ICUR distribution (first quartile, the median and third quartile in our analysis) and thus to lift the assumption that the regression coefficients are constant across the sample. Quantile regressions are especially useful in understanding outcomes that have non-linear relations with predictor variables or that are non-normally distributed, as it is the case for the ICURs in our sample. For all regression analyses, multicollinearity issues were investigated and acceptable VIF were found (<1.50). All regression analyses are performed using Stata 15@.

3. Results

3.1 Descriptive statistics

Table 1 provides the key summary statistics for the dependent and independent variables.

Table 1: Descriptive statistics

The obtained SMR is 'important' for 77.4% of the sample. Although 41.1% of the observations originally claimed an 'important' ASMR, only 5.5% obtained this level. The obtained ASMR is 'no therapeutic progress' and 'minor' for 20.5% and 36.3% of the observations, respectively. Almost three-quarter of the observations are drugs targeting life-threatening diseases. According to the classification of the CT, 24% of the observations correspond to drugs with a public health impact. Drugs with therapeutic alternatives constitute 79.5% of the observations and only 17.8% of the observations are drugs with a pediatric indication. The target population ranges from 30 to 1,011,505 patients with a mean of 47,830 patients. For the 68 cancer drugs, the primary endpoint is overall survival in 25 cases only, while a surrogate endpoint is used in 43 cases.

Claimed ICURs range from 622€/QALY to 4,345,650€/QALY with a mean of 287,821€/QALY. Regarding the distribution of the ICURs, the first quartile is at 51,447€/QALY, the median is at 112,328€/QALY and the third quartile is at 239,145€/QALY. Less than half (44.5%) of the ICURs claimed by the pharmaceutical firms were validated by the CEESP. The median ICUR is significantly higher for drugs targeting rare diseases compared to other therapeutic areas ($Z = -6.160$, $p < .001$), for drugs without alternative ($Z = 1.719$, $p = 0.0856$) and for drugs

targeting life-threatening diseases ($Z = -3.463$, $p = 0.0005$). The mean ICUR is also significantly higher for drugs with a pediatric indication ($t = -4.3836$, $p < 0.0001$). On the contrary, no significant differences are found in median ($Z = -0.390$, $p = 0.6969$) or mean ($t = 0.5225$, $p = 0.6023$) ICURs for drugs whose ICURs were validated or not.

3.2 Regression analyses on the obtained SMR and ASMR and on the claimed ICUR

Table 2 presents the regression analysis results for the obtained SMR.

Table 2: Results of the regression analysis for the factors associated with the obtained SMR

The severity of the disease is not significantly associated with the SMR. Drugs whose efficacy-adverse events balance is classified as 'intermediate' or 'important' tend to obtain higher SMR. On the contrary, drugs used for preventive or symptomatic purposes tend to obtain a lower SMR compared to curative drugs. Neither the public health impact nor the availability of alternatives is significantly associated with the obtained SMR. Table C1 in Appendix C provides supplementary analyses on the relative contribution of each criterion to the SMR classification. These analyses show that two criteria – the efficacy-adverse events balance and the drug function – have a strong discriminatory power whereas the three other criteria do not contribute to the SMR classification.

Table 3 presents the regression analysis results for the factors associated with the obtained ASMR.

Table 3: Results of the regression analysis for the factors associated with the obtained ASMR

The QALY gain of the drug is positively associated with its ASMR. On the contrary, the existence of therapeutic alternatives is not significantly associated with the ASMR. Drugs targeting life-threatening diseases tend to obtain a higher ASMR. The type of primary efficacy endpoint used is not associated with the ASMR. Lastly, results show a positive and significant association between the validation of the ICUR by the CEESP and the ASMR.

Table 4 presents the regression analysis results for the claimed ICUR. ICURs at the median and at the third quartile of the ICUR distribution are significantly lower, by 108,821€/QALY and 429,189€/QALY respectively, for drugs with therapeutic alternatives compared to drugs without alternative. At the third quartile of the ICUR distribution, the ICUR is significantly higher for drugs with a pediatric indication. Moreover, the size of the target population is negatively and significantly associated with the value of the ICUR at the first quartile of the ICUR distribution only. More specifically, a 1,000 increase in the size of the target population is associated with a 94.83€/QALY decrease in the value of the ICUR at the first quartile. The claimed ASMR is positively associated with the value of the ICUR at the first quartile of the ICUR distribution. At this point of the distribution, a €37,409 increase in

the value of the ICUR is observed when moving from a 'moderate' to an 'important' claimed ASMR. The value of the ICUR at the median of the distribution is significantly higher (by 85,293€/QALY) for drugs targeting life-threatening diseases.

Table 4: Results of quantile regression analyses for the factors associated with the claimed ICUR

4. Discussion

This retrospective analysis of the 2014-2020 HAS recommendations on innovative drugs provides three main results that are worth discussing in terms of the French HTA decision making process.

First, the study contributes to the analysis of the consistency and the transparency of the SMR and ASMR which are the two main composite indicators used in the clinical assessment. The issue at stake is the extent to which the SMR and ASMR obtained by innovative drugs actually reflect the official criteria included in these indicators.

Regarding the SMR, significant associations are found between the SMR obtained and only two of its official criteria, the efficacy-adverse events balance of the drug and the drug function. Moreover, the results underline the contrasting discriminatory power of the SMR criteria: the efficacy-adverse events balance has by far the highest explanatory power, whereas the severity and the public health impact criteria have none. These results are in line with the conclusions of the Polton's report (2014) which shows, based on all drugs assessed by the CT in 2014, that the SMR rating is mainly driven by the efficacy-adverse events criterion. Moreover, unlike Le Pen C, Priol G, Lilliu H. (2003) who found that disease severity was an important criterion in the determination of the SMR in the early 2000's, Polton, D (2014) found that this criterion was playing a secondary role in 2014. Our results seem to confirm the conclusion of the Polton's report as we also find that the disease severity criterion provides no contribution to the SMR obtained by innovative drugs in recent years. However, beyond differences in results, a common point between our study and those previously conducted by Le Pen C, Priol G, Lilliu H. (2003) and Polton, D (2014) is that the public health impact criterion always contributes little to the SMR rating obtained by new drugs.

Provided that they are confirmed by analyses conducted on a larger sample of drugs recently evaluated by the CT, our results on the SMR drivers seem to indicate the need for a reevaluation of the criteria considered to evaluate the clinical benefit of new drugs in France. Indeed, the discrepancies found between guidelines and practices

impair the transparency and the predictability of the French HTA procedure whereas the enforcement of official criteria are key to legitimate a prioritizing procedure [27].

The case of the public health impact criterion, which was found to have a low discriminating power in all studies conducted on reimbursement decisions of new drugs in France, calls for a specific comment on the consistency of the SMR rating. The public health impact criterion is based on elements that are potentially redundant with the other official criteria of the SMR. Indeed, its classification is officially based on the prevalence of the disease, the severity of the disease, and the existence of a relevant comparator. However, these last two factors are already directly considered as full-fledged criteria in the SMR rating process. It follows that a coherent treatment of the public health impact in the French HTA process would certainly lead to removing this criterion from the SMR and treating it as a separate criterion in the clinical evaluation.

As far as the disease severity criterion is concerned, our results echo the lack of transparency regarding the relative weight of this criterion in drug reimbursement decisions reported in the literature even in countries where it explicitly plays a role in reimbursement assessments [28]. Indeed, despite the official inclusion of disease severity as a criterion in the SMR rating in France, our results show that this criterion had no discriminating power in reimbursement decisions of innovative drugs in recent years. On the contrary, the disease severity criterion is significantly associated with the obtained ASMR. Thus, the disease severity appears as a main driving factor of the ASMR classification for innovative drugs in France, in line with HTA in other European [22,29] and non-European countries [23,30]. The change in the pharmaceutical environment, with the entry of a much higher number of new drugs on the French market as compared to the early 2000's, could explain that the weights of the SMR criteria have evolved over time, Polton's report argues. Nevertheless, beyond weighting considerations within the SMR indicator, our results also question the articulation and the complementarity between the SMR and the ASMR, especially regarding the disease severity criterion. Further empirical work is needed to document this important issue for the HTA process in France as the latter would certainly gain in consistency by explicitly fixing whether the disease severity criterion intervenes at the level of admission to reimbursement or at the level of price negotiation.

Regarding the ASMR, the results also show that no ASMR penalty is observed for cancer drugs using surrogates, instead of overall survival, as primary endpoints to measure clinical efficacy although relying on surrogates is known to increase the uncertainty around the effect size in terms of final outcomes relevant to patients [17-18]. In the perspective of a European harmonization of clinical assessments, the debate on the use of surrogates will have

to be settled and it is interesting to know, beyond the positions, the practices of each country to converge to a common evaluation framework.

Second, the paper documents how Economic Opinions, which were introduced into the French HTA process in 2013, are articulated with Clinical Opinions. Clinical and economic evaluations are indeed conducted independently in the assessment process of the HAS and the question arises as to whether they converge [31]. The results support the idea of a convergence in two ways. First, as previously documented for cancer drugs [32], the results show a consistency between the ordinal rating of the ASMR in the Clinical Opinions and the QALY gains in the Economic Opinions: the higher the QALY gain, the higher the ASMR obtained. Second, this dual assessment of the added value of innovative drugs does not lead to contradictory results since a positive association is found between the validation of the ICUR in the Economic Opinion and the ASMR obtained in the Clinical Opinion.

Third, the study contributes to fill the information gap on the ICURs of innovative drugs in France. The analysis provides a benchmark for acceptable levels of ICUR in the French setting but also shows how pharmaceutical firms are adapting to the regulations. Within all the innovative drugs entering the French drug market between 2014 et 2020, about a quarter of claimed ICURs are below the hypothetical threshold of 50,000€/QALY [33] and two thirds (79/123) are below the estimate for the value of statistical QALY (147,093€) recently calculated using the official French value of statistical life [34].

Finally, the quantile regression analysis allows to investigate how the factors associated with the ICURs claimed by the firms differ along the ICUR distribution: moving from the bottom to the top quartile, individual characteristic considerations related to the disease or to the population substitute themselves to health population level considerations. At the bottom of the ICUR distribution, on the one hand, the innovation premium associated with moving from a 'moderate' to an 'important' claimed ASMR appears significant. A negative association between the size of the target population and the ICUR level is also found. The anticipation of price/volume agreements, sometimes implemented by the CEPS in the price negotiations with pharmaceutical firms, could be an element of explanation for this negative association [35]. At the top of the ICUR distribution on the other hand, the drug value claimed by pharmaceutical firms embraces considerations which go beyond the level of innovation and includes specific characteristics related to the target population and the medical need. A higher collective investment is indeed asked by pharmaceutical firms in France for pediatric drugs and for drugs without alternative as shown by the positive associations we find between these drug characteristics and the value of the ICUR at the top of the ICUR distribution. For the former, the results are consistent with observed derogatory financing schemes

and ICUR thresholds used for pediatric drugs in some countries. In the UK, NICE for example considers pediatric drugs as a special circumstance when making judgments about cost-effectiveness [36]. Moreover, there is also empirical evidence that the general population gives more weight and expresses a higher willingness to pay for QALY gains among children [21,25]. A qualitative study on the reimbursement criteria carried out in four European countries, including France, showed that decision makers themselves tend to be more lenient on reimbursement decisions when the drugs target children or younger people [28]. As they tend to claim higher ICURs for pediatric drugs, our results seem to indicate that pharmaceutical firms anticipate the collective support from the decision makers and the public on this prioritization criteria. Regarding drugs with no therapeutic alternative, empirical studies have also shown that the public [24,37,38] and decision makers [20] give priority for the funding of treatment without alternative.

Two limitations of the study should be acknowledged. First, the interpretation of the results and the insights they provide on the French HTA procedure are conditioned by the sample used, which only includes drugs with claimed ASMR from ‘major’ to ‘moderate’ for which economic evaluation is mandatory. Second, it should be emphasized that ICURs used in the regression analyses are those claimed by pharmaceutical firms at the time they apply for reimbursement and then integrate the price of drugs before the negotiation with the CEPS. Studying the factors associated with the actual social willingness to pay for health gains in France would require recalculating the ICURs provided by the firms using negotiated prices, which unlike facial prices are not public, or to work with a different metric such as the cost per patient as was recently done in a study on the German HTA process [26]. Despite this limit, the analysis of the ICURs associated with the drugs recently accepted for reimbursement in France provides useful quantitative benchmarks to inform priority setting.

5. Conclusion

Based on a retrospective analysis of the HAS recommendations for innovative drugs from 2014 to 2020, this study identifies the criteria that are actually considered in the clinical assessment of drugs entering the French market. Discrepancies are found between guidelines and practices which impair the transparency and the predictability of the French HTA procedure. Our results also point to the consistency between the economic and clinical assessments of the added value of innovative drugs. The analysis provides a benchmark for acceptable levels of ICUR in the French setting.

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Variable name	Description	Modality	Mean	Frequency (%)	[CI 95%] ^a
Obtained SMR	Clinical benefit	Insufficient		14 (9.6%)	[5.74; 15.60]
		Mild		1 (0.7%)	[0.09; 5.77]
		Moderate		18 (12.3%)	[7.88; 18.78]
		Important		113 (77.4%)	[69.84; 83.51]
Obtained ASMR	Clinical added value (N= 132) ^b	No clinical improvement		30 (22.7%)	[16.32; 30.73]
		Minor		53 (40.2%)	[32.07; 48.80]
		Moderate		41 (31.1%)	[23.70; 39.53]
		Important		8 (6.1%)	[3.04; 11.72]
Claimed ASMR	Clinical added value claimed by the pharmaceutical company	Moderate		86 (58.9%)	[50.69; 66.65]
		Important		60 (41.1%)	[33.35; 49.31]
Claimed ICUR	ICUR level reported by the pharmaceutical firm (N= 123) ^b		287,821		[179,614; 396,028]
ICUR validation	ICUR validation by the economic committee (N=145) ^b	No		80 (55.2%)	[46.94; 63.13]
		Yes		65 (44.8%)	[36.87; 53.06]
Severity	Severity of the treated disease	Not life threatening		39 (26.7%)	[20.12; 34.53]
		Life threatening		107 (73.3%)	[65.47; 79.88]
Efficacy – adverse events	Efficacy-adverse events balance	Not or poorly established, Insufficient or Low		15 (10.3%)	[6.26; 16.40]
		Intermediate		24 (16.4%)	[11.23; 23.42]
		Important		107 (73.3%)	[65.47; 79.88]
Drug function	Function of the drug	Curative		87 (59.6%)	[51.38; 67.30]
		Preventive		32 (21.9%)	[15.90; 29.42]
		Symptomatic		27 (18.5%)	[12.96; 25.69]
Public health impact	Public health impact	No		111 (76.0%)	[68.37; 82.31]
		Yes		35 (24.0%)	[17.69; 31.63]
Alternatives	Existence of therapeutic alternatives	No		30 (20.5%)	[14.71; 27.94]
		Yes		116 (79.5%)	[72.06; 85.29]
Pediatric	Drug is used on under 18 years old patients	No		120 (82.2%)	[75.06; 87.62]
		Yes		26 (17.8%)	[12.38; 24.94]
Target population	Target population in thousands (N= 138) ^b	Mean (SD)	47.83		[20.01; 75.66]
Primary endpoint	Primary endpoint used in the clinical efficacy study	Overall survival for cancer drugs		25 (17.1%)	[11.80; 24.18]
		Surrogate endpoints for cancer drugs ^c		43 (29.5%)	[22.58; 37.41]
		Primary endpoints for non-cancer drugs ^d		78 (53.4%)	[45.25; 61.42]
QALY gains	QALY gains reported by the pharmaceutical firm (N= 114) ^b	Mean (SD)	1.40		[0.8089; 1.9994]

^a CI=confidence interval. For categorical variables the confidence interval corresponds to the proportions in percentages.

^b N=146 except when otherwise indicated. The ASMR is missing for 14 observations for which an insufficient SMR was given by the CT. The target population is only available in 138 Clinical Opinions. ICUR levels, ICUR validation and QALY gains are not publicly available in all the Economic Opinions.

^c progression-free survival (PFS), disease-free survival (DFS), metastasis-free survival (MFS), overall response rate (ORR) and percentage of patients with overall remission.

^d includes, for example, the variation in the walking perimeter on the 6-minute walk test; the variation in the number of migraine days per month; overall response rate (ORR); number of hereditary angioedema crisis confirmed by the investigators in monthly rates; variation of the Multi-Luminance Mobility Test score...

Table 1: Descriptive statistics

		Obtained SMR
		Odd ratio
		(90% confidence interval)
Severity (ref: not life threatening)	Life threatening	0.9119 (0.2858, 2.9097)
Efficacy – adverse events balance (ref: not established, insufficient or low)	Intermediate	51.6011** (3.9748, 669.8938)
	Important	8330.595*** (130.9538, 529948.8)
Drug function (ref: curative)	Preventive	0.0469*** (0.0087, 0.2519)
	Symptomatic	0.0464*** (0.0133, 0.1623)
Public health impact (ref: no)	Yes	3.0718 (0.9984, 9.4511)
Alternatives (ref: no)	Yes	1.0069 (0.3036, 3.3396)
Observations		146
Pseudo R2		0.67

* p<0.10, ** p<0.05, *** p<0.01

Table 2: Results of regression analysis for the factors associated with the obtained SMR

		Obtained ASMR
		Odd ratio (90% confidence interval)
Primary endpoint (ref: overall survival for cancer drugs)	Surrogate endpoints for cancer drugs	1.9582 (0.7175, 5.3444)
	Primary endpoints for non-cancer drugs	0.4535 (0. 1140, 1.8034)
Alternatives (ref: no)	Yes	1.0575 (0.3192, 3.5039)
Severity (ref: not life threatening)	Life threatening	11.1442*** (3.0124, 41.2271)
QALY gains		1.6257*** (1.2697, 2.0815)
ICUR validation (ref: no)	Yes	2.5793** (1.2170, 5.4667)
Observations		104 ^a
Pseudo R2		0.25

* p<0.10, ** p<0.05, *** p<0.01

^a the number of observations is 104 due to missing values for the QALY gains and the ASMR rating

Table 3: Results of regression analysis for the factors associated with the obtained ASMR

		Claimed ICUR		
		First quartile	Median	Third quartile
Alternatives (ref: no)	Yes	-14069.4 (-0.78)	-108821.1** (-2.46)	-429189.5* (-1.85)
Pediatric (ref: no)	Yes	-1329.1 (-0.07)	47878.7 (0.96)	1361801.2*** (5.24)
Target population (thousands)		-94.83** (-2.17)	-96.88 (-0.90)	-235.4 (-0.42)
Claimed ASMR (ref: moderate)	Important	37409.6** (2.60)	-6192.4 (-0.17)	-74478.5 (-0.40)
Severity (ref: not life threatening)	Life threatening	18828.1 (1.11)	85239.2** (2.04)	194986.2 (0.89)
Constant		54767.6*** (2.80)	150141.3*** (3.12)	500872.5** (1.99)
Observations		115 ^a	115 ^a	115 ^a
Pseudo R2		0.06	0.04	0.14

t-statistics in parentheses. * p<0.10, ** p<0.05, *** p<0.01

^a the number of observations is 115 due to missing values for the ICUR level and the size of the target population

Table 4: Results of quantile regression analyses for the factors associated with claimed ICUR