1 Supplementary Material

Methodology

A review was conducted of NHAs-reports of approved ATMPs published by the following national bodies: National Centre for Pharmacoeconomics; NCPE (Ireland), National Institute for Health and Care Excellence; NICE (England/Wales), Scottish Medicines Consortium; SCM (Scotland), National Health Care Institute, Zorginstituut Nederland (Netherlands), Haute Autorité de Santé; HAS (France), Gemeinsamer Bundesausschuss; G-BA and Institute for Quality and Efficiency in Health Care; IQWiG (Germany), Spanish Ministry of Health, Comisión Interministerial de precios de medicamentos (CIMP) minutes (Spain) and Agenzia Italiana del Farmaco; AIFA (Italy).

The type of HTA report that has been used for the analysis is as follows: for Ireland the National Centre for Pharmacoeconomics (NCPE) Technical Summary report, for England/Wales the NICE technology appraisal, for Scotland the Scottish Medicines Consortium assessment/appraisal, for Netherlands the Summary of recommendations by Zorginstituut Nederland (National Health Care Institute), for France the AVIS report launched by Hauté Autorité de Santé (HAS), for Germany the Justification and Resolution reports of the Federal Joint Committee (G-BA), for Italy the AIFA Report Tecnico and for Spain the available information is published in BIFIMED.

Determination of product´s added therapeutic value

The determination of product´s added therapeutic value (ATV) has different implications in terms of recommendations, reimbursement negotiations and granting the drug innovativeness status.

In France, the HAS assesses the ATV or the called clinical added value (CAV) on a 5-point scale for pricing negotiations based on clinical data. The CAV is an assessment to measure the added value of

the medicine compared with existing therapies and the punctuation is determined by i) the quality of the data, ii) the clinical relevance of product´s effect compared to the comparator, with special emphasis on the magnitude of quality of life (QoL), and iii) the medical need in the indication assessed [1]. A major to moderate CAV leads to the highest prices, a minor CAV leads to a higher price than the comparator, and no CAV leads to lower price than the cheapest comparator [2].

The Italian Medicines Agency introduced in 2017 a process to appraise innovativeness of medicines. Innovativeness status allows speeder market access and dedicated funds (one for cancer medicines and the other for non-cancer medicines). To obtain this status, which can be attributed only to drugs indicated for serious illnesses (life-threatening diseases; diseases producing frequent hospitalisations or causing disabilities that can seriously compromise quality of life), three criteria are assessed: therapeutic need, added therapeutic value and robustness of the scientific evidence submitted by the company [3,4,5]. The added therapeutic value can be rated in 5 categories (Table 2): maximum, important, moderate, poor and absent.

In Germany, the term "benefit" is defined as an "effect" and the term "added benefit" is defined as such an effect compared with the appropriate comparator therapy providing a higher quantitative or qualitative benefit [6]. The probability of the existence of an effect is examined for each outcome separately leading to a qualitative conclusion and depending on the quality of the evidence, the probability is classified as a hint, an indication or proof [7,8,9]. In the second step, the extent of the effect size is determined for each outcome to draw quantitative conclusions, which are classified as: major, considerable, minor, and non-quantifiable. The overall conclusion on the added benefit is determined on the basis of all outcomes according to the 6 grades taking into account the probability and extent at outcome level [7,8]. The benefit for patients is assessed considering improvements in health status, reductions in the duration of the disease, survival gains, the reduction of side-effects and improvement in quality of life [10]. If the G-BA decides that the new medicinal product does not

have any additional benefit over the appropriate comparator, it will be included in the reference price system, and if the drug without additional benefit cannot be allocated to a reference price group, a reimbursement price will also be agreed on [11].

In Netherlands, a new drug can be considered as a "substitutable" if it has similar therapeutic value or "non-substitutable" if the product has an added therapeutic value. This classification will have an impact on the type of reimbursement; the price of "substitutable" drugs will be calculated based on the similar prices for the products within the same cluster, while the ones with added therapeutic value will not be included in the common reimbursement system and the reimbursement will be decided based on magnitude of the added value and the cost-effectiveness evaluation [12]. For a drug to be included in the insurance package must comply with the "established medical science and medical practice" statuary criterion, which is assessed by determining the relative effectiveness in comparison to the standard or usual treatment [13].

The Scottish Medicines Consortium (SMC) committee uses the clinical checklists that summarise the key strengths and weaknesses to decide on drug reimbursement but there is no separate assessment of ATV. The methodological quality of the study, the appropriateness of the population, the relevance of clinical endpoints (including HQoL endpoints), the safety profile, the potential place of the medicine within the disease context and with respect to key comparators and any unmet need, among other factors are evaluated to determine the clinical effectiveness and therapeutic value of the drug [14]. In addition, for medicines used at the end of life and for very rare conditions, the sponsor may ask for the drug to be considered at a Patient and Clinician Engagement (PACE) meeting. PACE process gives the opportunity to patient groups and clinicians with regards to the added value of a medicine which may not always be captured in the company's submission and this output has a major weight on SMC decision making [15].

In Spain, the degree of innovation and the therapeutic and social value of the medicine is one of the key factors for the reimbursement decision-making, but there are no formal criteria for linking price to ATV. In Ireland, there are also no grades to determine the ATV and the clinical effectiveness assessment are the main tool to compare the new drug with the best SoC [16]. In England, the ATV is more related with the health-economic analysis by the number of Quality Adjusted Life Year (QALY) gained [17,18].

Some examples of alignment of differences among countries are discusses as follows.

In the first assessment of Kymriah® for diffuse large B-cell lymphoma indication (2019), Netherlands HTA did not recognise any ATV under the opinion that it was uncertain whether there was a clinically relevant difference in the overall survival compared to salvage chemotherapy (plus a stem cell transplantation). In the same line, in Germany it was considered that there was lack of proof of additional benefit since the data from the registries were insufficient for comparability between populations and due the observation periods were considered short. In contrast, Italy considered the rates of ORR and CR observed in the pivotal study to be of clinical relevance, even if did not constitute an evident superiority with respect to therapeutic alternatives. The clinical relevance of the results with respect to possible comparators was found in the duration of the observed response compared to published projections suggesting the possibility of real long-term disease control. Finally, in France, in line with Netherlands, it was considered that the quantification of the clinical effect was difficult since no comparative studies with usual management were presented. Similarly happened for the other Kymriah®´s indication (acute lymphoblastic leukemia), but in this case, in Netherlands the data on survival was considered as clinically relevant in comparison with the one reported in the literature, and in France a higher ATV rated was assigned due to efficacy data showing a high percentage of complete remissions at 3 months (about 67% of the intended-to-treat population) maintained in approximately 40% of patients after a median follow-up of 9 months.

For Zolgensma®; in Italy although there was a lot of critical gaps found, e.g., sample size, product quality etc., it was considered that the product had the potential to modify the natural course of the disease. In France, Netherlands and Germany it is considered that nusinersen would be the reference comparator and no comparative data was available, but while in France and Italy the ATV was only accepted for certain types of SMN mutations, in Netherlands the "state of science and practice" was considered met for all subtypes.

Aligned assessment can also be seen for Luxturna®; Italy considered that the ATV was important since data demonstrated clinical improvement maintained after 4 years, in France it was considered that the benefit at one year was already significant and in Germany data for after 3 years after baseline was available at the time of the assessment. Although in Netherlands it was considered that there was no recovery of normal vision and it was not clear how long the effect could last, it was noted the importance of halting the disease, which mean that the patient will remain self-sufficient longer.Aligned assessment can also be seen for Luxturna®; Italy considered that the ATV was important since data demonstrated clinical improvement maintained after 4 years, in France it was considered that the benefit at one year was already significant and in Germany data for after 3 years after baseline was available at the time of the assessment. Although in Netherlands it was considered that there was no recovery of normal vision and it was not clear how long the effect could last, it was noted the importance of halting the disease, which mean that the patient will remain self-sufficient longer.

Special funding process that impact on reimbursement decision

Most countries have special funding processes for reimbursement decisions related to orphan drugs, drugs target to treat patients in their last months of life (also called end-of-life medicine), the disease severity and/or to cover an unmet medical need.

In France, for those orphan drugs where there is therapeutic value and budget impact lower than €30 million a full reimbursement is granted [19.] In Ireland, in the case of orphan drugs and cancer drugs, additional review committee advises on any additional benefit provided by the drug that may not have been captured as part of the HTA process. However, it has not been stablished if there is a correlation between this committee and positive recommendations [20]. In Scotland, ultra-orphan process provides reimbursement for a period of up to three years on the condition that further clinical effectiveness data are gathered. After this period, a reassessment is performed to decide on routine use of the medicine [21,22,23.] In Germany, the additional benefit for orphan medicines is considered to be already proven by the marketing authorisation, although manufacturers have to demonstrate the level of the additional therapeutic benefit in any case [10,24]. In Italy, for drugs that target rare diseases the "fully innovative" status is granted even with low quality of clinical evidence 5. In Netherlands, for orphan drugs, or drugs approved under a conditional or exceptional approval for which there might not be sufficient data to prove this effectiveness, an inclusion in the basic health insurance is possible. This scheme allows carrying out further research into the effectiveness and appropriate use during a period no longer than 7 or 14 years. The patients are obliged to participate in the research in order to be eligible for reimbursement [25.] There are special research funds to cover orphan drugs in Spain and Italy [24] and for the later those drugs that obtain the innovative status are funded through dedicated national funds for innovative oncological and non-oncological medicines to provide immediate access to eligible patients [26,27.] In England, the stablished criteria for end-of-life medicines by NICE includes that the treatment can offer an extension of life of at least 3 months, compared with current NHS treatment, and there is sufficiently robust data from progression-free survival or overall survival [28]. There is no additional flexibility in the case of orphan drugs, but NICE can evaluate certain type of drugs that meet several criteria under the Highly Specialised Technology evaluation (HST) process. NICE has set higher cost-effectiveness threshold in the case of for treatments that meet end-of-life criteria or for those very rare conditions evaluated as part of the HST procedure (see

below) [29]. In Scotland, there might also be a greater flexibility in terms of a higher cost per QALY for end-of-life medicines [30] and Ireland has also set a higher threshold for medicines for ultra-rare indications [31,32].

Time to market access

The reimbursement procedure itself should take no more than 90 days with a maximum of 180 days, as required by the European Transparency Directive (Directive 89/105/EEC of 21 December 1988). However, this deadline is variable given that does not consider the "clock stops" to allow the company to answer questions [33]. In England, when NICE recommends a treatment to be funded by the National Health System, the regulations require that the period within which the health service must comply will be stated in the recommendations as 3 months, except when particular barriers to implementation within that period are identified [34]. According to WAIT Efpia Indicator study, there is a high variability on patient access to new medicines across Europe, with a 90% variance between Northern and Western European countries and Southern and Eastern European countries. It has been studied that the average time between market authorisation and patient access presents a variability across Europe, from as little as 4 months to 29 months (over 2.5 years) [35].

Comparators used for the cost-effectiveness analysis, notified prices and incremental cost-effectiveness ratio

In England, NICE has set a cost-effectiveness threshold of £20,000–£30,000 per quality-adjusted life year (QALY) gained for a medicine to be reimbursed, £50,000 per QALY gained for treatments that meet end-of-life criteria and a threshold of £100,000 per QALY gained for those very rare conditions evaluated as part of the HST procedure [29]. The SMC has not specific threshold but refers to this NICE threshold of £20,000 [31]. Ireland has set a threshold of €45,000 per QALY gained and €100,000 for medicines for ultra-rare indications [31,32]. In Netherlands, there are three burden-of-illness

categories with increasing ICERs based on the severity of the disease. The lowest threshold for low burden conditions is €20,000 per QALY gained [31]. In France and Italy, no established threshold in terms of incremental cost per QALY or per life-year gained is employed [36,37,38]. In Germany, the "efficiency frontier method" is used to determine an acceptable "value for money" [38,39]. Finally, in Spain a €24,000 per QALY threshold has been unofficially reported [38].

Appendix Table 1. Comparators used to determine the cost-effectiveness analysis of the approved ATMP

		Scotland	Ireland	England & Wales	The Netherlands	Italy	France	Germany
GTMP	Glybera®							Unknown
	Imlygic®			Best supportive care and dacarbazine				Unknown
	Kymriah® (ALL)	Fludarabine, cytarabine and idarubicin (FLA-IDA). Blinatumomab in sensitivity analysis	Blinatumomab and Fludarabine with idarubicin (FLA-IDA)	Blinatumomab and salvage chemotherapy. Blinatumomab preferred as a main comparator	Cost compared with blinatumomab	Salvage chemotherapy	Blinatumomab and salvage chemotherapy. *Blinatumomab as a main comparator*	Unknown
	Kymriah® (DLBCL)	Salvage chemotherapy	Salvage chemotherapy	Salvage chemotherapy	-	Salvage chemotherapy	Salvage chemotherapy	Unknown
	Yescarta®	Chemotherapy used in SCHOLAR-1 study	Salvage chemotherapy	Salvage chemotherapy with or without rituximab	-	BSC	Salvage chemotherapy with rituximab	Unknown
	Tecartus®	SOC		SOC: rituximab, bendamustine, and cytarabine (R-BAC)				
	Strimvelis®			Haematopoietic stem cell transplants (HSCTs) from an HLA-matched unrelated donor				
	Luxturna®	BSC	BSC	BSC	-	Unknown	BSC	Unknown
	Zynteglo®				Not specified		BSC (transfusions and iron chelators)	Unknown
	Zolgensma®	Nusinersen and BSC for pre-symptomatic patients	Nusinersen and BSC for pre-symptomatic patients	BSC	Nusinersen and BSC for pre-symptomatic patients	Nusinersen	Nusinersen and BSC	Nusinersen
	Libmeldy®							BSC
SCTMP	Provenge®							SOC
	Zalmoxis®					Unknown		
	Alofisel®	Surgical examination under anaesthesia +/- seton placement plus curettage	Surgical examination under anaesthesia +/- seton placement plus curettage			Unknown	Unknown	
TEP	Chondrocelect®			Microfacture	Microfacture		Unknown	
	MACI®			-				Unknown
	Spherox®			Microfracture for defects up to 2 cm2 and BSC for defects larger than 2 cm2			Microfractures "plus" technique (combined with insertion of a membrane) is used for	Unknown

						defects > 2 cm2 whereas the osteochondral allograft technique is reserved for very extensive (> 4 cm2) and deep defects.	
Holoclar®	BSC		Conjunctival limbal autograft, keratolimbal allograft and BSC		Unknown	Unknown	Unknown

Colour code: green (economic analysis performed), orange (no economic analysis performed). For Spain no information on the cost-effectiveness analysis is public. No information is available yet for Abecma® in any country. BSC: best supportive care; GTMP: gene therapy medicinal products; SCTMP: somatic-cell therapy medicinal product; SOC: standard of care; TEP: tissue engineered medicinal product.

Appendix Table 2. Key considerations that influenced the reimbursement decision

EUnetHTA Domain	Key considerations
Gene therapies (CAR-T products)	
Health problem and current use of technology	Offers a new treatment option
	High unmet need in these patients; limited treatment options and no standard treatment
	Treatment options are limited, often poorly tolerated and at best produce short remissions for the majority of patients
	Therapeutic advancement due to its different mode of action and considerable clinical benefit
	Likelihood of having an impact on public health
	Burden both on individuals and on society caused by the health problem
Patient and social aspects	Disease can have a huge emotional, physical and financial impact on both the patient and their families
	For patients and their families, the emotional and financial burden associated with this life-threatening illness could be reduced
	Devastating disease with significant symptoms and an extremely poor prognosis
	Available treatments with significant adverse events and are time intensive for patients
	Single infusion, versus several rounds of treatment involved in chemotherapy and allogenic stem cell transplants, may be preferable to patients and families/carers
	Patients who respond may be able to resume work, education, self-care and social activities
	Improvements in a patient's condition and prognosis will also have a wider impact on the lives of their family and friends
	Product need to be delivered by appropriately trained medical and nursing teams in a unit with access to intensive care and strict monitoring
	Impact on the service due to specialist requirements for manufacture, administration and monitoring (e.g., additional consultant and medical support, specialist nursing pharmacy and laboratory staffing)
Clinical Effectiveness	Clinical meaningful results compared to historical control
	Data available suggest that long term remission could potentially lead to many years of life gained or might be curative
	Study results are generalisable to patients in the EU country
	The treatment is clinically effective, but the benefit cannot be quantified because of the immature survival data and lack of trial data compared with SoC
	Insufficient evidence on comparative efficacy; single arm study with no control arm
	In the country, there is established clinical experience of using CAR-T cell therapies
	Indirect comparison: differences across the studies in design, baseline characteristics, maturity of data, measurement of outcomes and sample sizes
	No comparative data, naïve indirect comparison performed. This indirect comparison might be acceptable, but was subject to uncertainty as a result of the differences in the trial populations
	The study was open-label, there is a potential for bias
	Immature clinical data
	Quality of the evidence will remain very low even with a longer follow-up duration
	The relevant comparator, SoC, for the disease is not well defined
	Uncertainties around the comparator in relation to country practice
	Data on patient reported quality of life outcomes are very limited to a small proportion of patients
	Heterogenicity between historical control population and population included in the pivotal trial
	Uncertainty around the generalisability of the results to clinical practice
	The indirect comparison did not include health related quality of life outcomes
	Due to a lack and immaturity of clinical data there is high uncertainty over the durability of benefit
	Longer term data insufficient to confirm curative treatment or sustained responses
	Uncertainties associated to the effectiveness of re-treatment
Safety	Insufficient evidence on comparative safety; open-label and uncontrolled study limits the assessment of safety

EUnetHTA Domain	Key considerations
	The indirect comparison did not include safety
	Longer term safety data are as yet unavailable
Cost- and economical evaluation	The company's model is acceptable for decision-making
	The economic analysis based on a naïve indirect comparison
	The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise
	Budget impact and concerns that increasing experience with administration of CAR-T cells or adding new indications, which may lead to greater numbers of patients being treated and therefore, a greater budget impact
	Methodological quality of the analysis of cost-effectiveness supplied by the manufacturer is inadequate.
	Lack of directly comparative data and thus the economic analysis uses an indirect comparison method, which has a range of weaknesses
	There is no cost-effectiveness model of sufficient quality available
	The model has a long-time horizon relative to the limited available data on treatment, and thus there will be uncertainty associated with the extrapolations used
	Uncertain assumptions applied to the cost-economic model
	Cost-effectiveness needs to be improved relative to existing treatments
	Lack of comparison between CAR-T therapies on the same indication
	Uncertain whether long-term survivors have the same health-related quality of life as people in the general population of the same age and sex
Gene therapies (viral vector- or cell- based therapies)	
Health problem and current use of technology	The treatment offers a new treatment option
	High unmet need in these patients; limited treatment options and no standard treatment
	The condition severely affects the quality of life of people with the condition
Patient and social aspects	Rare, serious, life-threatening and debilitating condition that also severely affects the lives of families and carers
	Patients who respond may be able to resume work, education, self-care and social activities
	Patients who respond could potentially have less disability burden over time
	Inherited nature of the condition; emotional toll attached to passing on or being at risk from a genetic disorder.
	Condition can affect opportunities in education, the labour market, and in day-to-day life
	Improvements in a patient's condition and prognosis will also have a wider impact on the lives of their family and friends
	Single infusion: It is a one-off treatment, which could be an advantage to patients and their families/carers
	Improvements to carer-related quality of life should be qualitatively taken into consideration in the committee's decision-making
	Service implications: in determining patient eligibility for treatment including genetic testing, infrastructure and subsequent monitoring of patients
Clinical Effectiveness	Substantial improvement in quality of life
	Significant clinical benefit compared to the control group (historical control or not)
	There is a biological rationale for the treatment effect to be maintained
	The primary endpoint that has not been validated and is potentially prone to bias, it is but acceptable endpoint because it captures a relevant clinical effect of the treatment
	No direct measure of HRQoL used in the clinical trials, considered that the lack of patient reported outcomes was a key limitation in the evidence
	High level of uncertainty relating to longer-term clinical effectiveness. Longer term data insufficient to confirm curative treatment or sustained responses
	Lack of QoL assessment or unclear how improvements in activities of daily living observed relate to QoL for patients
	No information on whether patients who may lose treatment effect would benefit from retreatment
	There is some uncertainty over what represents a clinically relevant improvement (in terms of primary endpoint)
	The overall treatment effect may not be generalisable in terms of benefit : risk ratio in individual patients
	Unclear what factors make some patients more likely to respond to treatment
	Heterogenicity between (historical) control population and population included in the pivotal trial
	Uncertain the relevance of the study results to clinical practice in other subgroups of patients with different disease grades/types/age

EUnetHTA Domain	Key considerations
	The type of treatment received in the trial differed from what would be available for patients in clinical practice today
	The natural history studies all had limitations, apart from being either exclusively or primarily based in the US, where there is a different approach in the BSC vs the EU countries
	Clinical-effectiveness data came from a small number of people and that follow-up data were limited
	The population under consideration was based on and derived solely from an analysis of an exploratory post-hoc subgroup
Safety	Safety data were only available for small patient numbers
	Longer term safety data are as yet unavailable
	Treatment generally well tolerated but potential risks and complications associated to the intervention
Cost- and economical evaluation	The pharmaco-economic analysis presented was comprehensive and the reporting was thorough and transparent
	The model was considered generally suitable for decision making, incorporating relevant health states and capturing fairly well the impact of disease progression on relevant costs and health outcomes important to patients
	The methods utilised in the modelling were generally robust
	The company presented an extensive and comprehensive list of sensitivity analyses which captured the uncertainty around the base case results reasonably well
	A model-based economic evaluation projected a substantial gain in quality-adjusted life years compared to best supportive care
	The economic analysis based on a naïve indirect comparison
	Analysis performed with a comparator chosen by the Applicant, while the HTA consider other comparator as more relevant
	Uncertain assumptions applied to the cost-economic model
	Uncertain assumptions applied to the cost-economic model in terms of long-term effects
	Budget impact: treatment's cost in relation to its health benefits remains high
	Budget impact: uncertainty associated with the Applicant's estimated on number of patients eligible to the treatment (incidence rate)
	The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise
	The study suffered from a number of limitations in terms of its applicability to the modelled population
	Uncertainty around the health-state utilities used in the model and that they had major effect on estimates of cost effectiveness
	The proxy health utility scores utilised were based on a very small sample of clinician responses and are subject to a number of limitations
	The primary outcome was not used in the economic evaluation as no data were available linking this outcome to costs, utilities or mortality and no data on the long-term change in this outcome were available either
	Considerable limitations to the modelling approach and methodology and the data used to inform the model
	The lack of suitable effectiveness inputs in the economic model prevented the committee from calculating a plausible incremental cost effectiveness ratio
Cell- and tissue-engineered therapies	
Health problem and current use of technology	Considered therapeutic advancement
	Innovative technology which may offer the prospect of long-term healing
	Disease can be life-changing and severely debilitating condition
	The treatment is well tolerated and would provide another treatment option before invasive surgery
	Current treatment options are limited and suboptimal. There is no standardised treatment
Patient and social aspects	Disease can have a huge emotional, physical and financial impact on both the patient and their families
	Often diagnosed in younger patients who may subsequently have a lifetime of disease burden
	Service implications: training on administering as well as for training staff in the appropriate preparation
Clinical Effectiveness	Trial populations are generalisable to patients likely to be seen in the respective EU country
	Evidence shows that the treatment offered several advantages over existing treatments.
	Clinical results showed only a modest improvement in the proportion of people achieving complete remission compared with placebo
	Natural disease study does not contribute significantly to predicting the clinical effectiveness of treatment in clinical practice
	Indirect clinical evidence from a network meta-analysis is not relevant because the comparators are not licensed in the country
	Study results may not be generalisable to the treatment of patients in clinical practice

EUnetHTA Domain	Key considerations
	Not clear how optimising the use of concomitant treatment would affect the generalisability of the study results to clinical practice
	The study was open-label and retrospective, there is a potential for bias
	Substantial uncertainty regarding the long-term clinical effectiveness
	Substantial uncertainty regarding the long-term clinical effectiveness compared to the SoC
	Heterogenicity between compared populations
	The treatment effects/results observed in the placebo group do not reflect country clinical practice, and therefore it is uncertain whether the treatment-benefit shown in the trial would translate to the same benefit over and above standard care in that country
	The pivotal did not collect patient-reported health-related quality of life data
Safety	Longer term safety data are as yet unavailable: long-term study are required to address missing data
	Lack of safety data in children and patients aged more than 65 years
Cost- and economical evaluation	The company's model structure is appropriate and suitable for decision making
	Only better data on long-term outcomes from the ongoing trial, or more robust information on the natural history of the disease, would make it possible to decide which is the most plausible ICER
	Company did not present a sufficiently robust economic analysis to gain acceptance
	W52 outcomes were assessed on a post hoc basis and this outcome was not included in the original study design, the risk of a false positive finding may be inflated and the results may be less robust
	The plausibility of certain estimates used in the study, considered uncertain given the absence of robust clinical data
	Even though utility values were not a significant driver of cost-effectiveness in the analysis, the different sources do introduce uncertainty in the model
	The lack of observed long-term data also contributes to uncertainty in estimates of other parameters in the model
	The extremely high upfront acquisition cost for this single-dose treatment is likely to have significant service implications and is associated with financial risk to the service if the long-term predicted clinical benefits do not materialise
	There was a high level of uncertainty with the clinical effectiveness evidence and as a result it was difficult to decide the most plausible estimate of cost effectiveness
	Considerable limitations to the modelling approach and methodology and the data used to inform the model
	Uncertain assumptions applied to the cost-economic model, also in terms of long-term effects

BSC: best supportive care; EU: European; SoC: standard of care; QoL: quality of life.

+: influences positively, -: influences negative

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