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Cost-utility of oral methylprednisolone in the treatment of multiple sclerosis relapses: results from the COPOUSEP trial

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### **Competing interest**

DV and RW received grants from the French Health Ministry, the Ligue Française contre la SEP and TEVA during the conduct of the study. ELP reports personal fees from Biogen, Roche, Merck, Novartis, Sanofi-Genzyme outside the submitted work. GE reports research grants from Merck, Biogen, Teva Pharma, Novartis, Roche and Sanofi, and personal fees from Biogenidec, Sanofi and Novartis outside the submitted work. DL reports personal fees from Biogen, Merck and Novartis, grants and personal fees from Roche, MedDay and Sanofi-Genzyme, and grants from Fondation ARSEP, outside the submitted work. FZ, MC, SW, CL, MM and KC have nothing to disclose.

### **Author contributions**

MM participated in designing the economic evaluation, carried out the economic analyses and interpretation of data, drafted the initial manuscript, and reviewed and revised the manuscript.

KC played a major role in conceptualizing and designing the economic study, supervised the economic analysis, interpreted the data, and reviewed and revised the manuscript.

DV participated in the literature search, conception, study design, statistical analysis, data interpretation, and manuscript writing of COPOUSEP trial. He participated in the literature search, and designing the economic evaluation, in interpretation of data and reviewed and revised the manuscript submitted.

ELP performed the literature search, participated to conception, study design, statistical analysis, data interpretation, and wrote the manuscript of COPOUSEP trial. She also participated in interpretation of data and reviewed and revised the manuscript submitted for the economy study.

GE participated in enrolment of patients, data gathering, analysis, and interpretation, and revision of the report. He also revised the manuscript submitted for the economy study.

DL, RW, CL, FZ, SW, VD, and MC participated in enrolment of patients, data interpretation, and writing the manuscript for the COPOUSEP trial.

All authors have approved the final version of the manuscript and its submission.

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## **Abstract**

**Background:** Studies have shown that oral high-dose methylprednisolone (MP) is non-inferior to intravenous MP in treating multiple sclerosis relapses in terms of effectiveness and tolerance. In order to assist with resource allocation and decision-making, its cost-effectiveness must also be assessed. Our objective was to evaluate the cost-utility of per os high-dose MP as well as the cost-savings associated with implementing the strategy.

**Methods:** A cost-utility analysis at 28 days was carried out using data from the French COPOUSEP multicenter double-blind randomized controlled non-inferiority trial and the statutory health insurance reimbursement database. Costs were calculated using a societal perspective, including both direct and indirect costs. An incremental cost-effectiveness ratio was calculated and bootstrapping methods assessed the uncertainty surrounding the results. An alternative scenario analysis in which MP was administered at home was also carried out. A budgetary impact analysis was carried at five years.

**Results:** In the conditions of the trial (hospitalized patients), there was no significant difference in utilities and costs at 28 days. The incremental cost-effectiveness ratio was €15,360 per quality-adjusted life-year gained. If multiple sclerosis relapses were treated at home, oral MP would be more effective, less costly and associated with annual savings up to 25 million euros for the French healthcare system.

**Conclusions:** Oral MP is cost-effective in the treatment of multiple sclerosis relapses and associated with major savings.

**Key words:** Multiple Sclerosis; Methylprednisolone; Oral administration; Cost-utility analysis

## **1. Introduction**

Multiple sclerosis (MS) is associated with a high economic burden, with studies reporting annual costs per patient varying between 11,900 and 57,500 euros [1–4]. Because the disease targets adults of working age it is also associated with productivity losses: unemployment rates in individuals with MS have been shown to be as high as 80% [5].

Relapses have a significant impact on patients' and carers' quality of life [6–9]. They also impact the cost of MS as treatment usually requires an admission to hospital [3,10] but the few studies available on the matter are limited by methodological flaws, such as relying on declarative data to identify relapses [11–13].

High-dose corticosteroids have proven effective for treating relapses [14–17] and until recently intravenous (IV) administration was the reference, requiring a hospitalization or at-home nurse care [18], which further contributed to the economic burden of MS [4]. In 2015, the COPOUSEP trial [19] demonstrated that per os (PO) high-dose methylprednisolone (MP) was not inferior to IV MP at 28 days in the treatment of MS relapses in terms of effectiveness and tolerance, confirming the results of previous less powered trials [20,21]. The absence of difference on relapse recovery was sustained up to six months of follow-up.

While one cost-minimization study found that oral MP led to significant cost-savings [22], it did not take into account the fact that oral MP could lead to a better outcome in terms of quality of life. As such, our objectives were to evaluate the cost-utility at 28 days of PO high-dose MP versus IV therapy in treating MS relapses as well as the cost-savings associated with implementing the PO strategy on a wider scale over a five-year period.

## **2. Materials and methods**

### *2.1 Study design*

COPOUSEP was a multicenter randomized double-blind non-inferiority French trial whose results were published in 2015 (ClinicalTrials.gov number: NCT00984984) [19]. Briefly, patients were

allocated to either PO or IV MP, 1000 mg once a day for 3 days. Both IV and PO MP were administered during a hospitalization. The trial was done in accordance with the International Conference on Harmonisation Guidelines for Good Clinical Practice and the principles of the Declaration of Helsinki. Local ethics committees approved the protocol and all patients provided written informed consent at enrolment.

## *2.2 Study population*

Patients aged 18–55 years with relapsing-remitting MS who reported a relapse within the previous 15 days with an increase of at least one point in one or more scores on the Kurtzke Functional System Scale were included in the COPOUSEP trial between January 2008 and June 2013 [19]. Patients with an available primary endpoint were included in the economic evaluation.

Patients were probabilistically matched with themselves in the *Système national d'information inter-régimes de l'Assurance maladie* (SNIIRAM) database (now *Système national des données de santé*, SNDS). This database records all resources reimbursed by the French statutory health insurance (SHI) using a single national anonymous identification number for each patient [23]. Access to the SNIIRAM database was granted by the French governing body on data protection (CNIL authorization number n° 1583678).

## *2.3 Effectiveness criteria*

Quality-adjusted life-years (QALYs) were calculated at 28 days using the EQ-5D-3L questionnaire at baseline and 28 days. QALYs correspond to life expectancy weighted down by patients' quality of life: a year in perfect health is equal to 1 QALY, while a year spent in less than perfect health will correspond to something lower than 1.

The EQ-5D-3L is a generic quality-of-life questionnaire which explores five dimensions: mobility, self-care, usual activities, pain/discomfort and anxiety/depression, each with three levels: no problem, some problems, and extreme problems. Patients' answers reflect their health state and are



converted into utility weights using French reference values, varying from 1 (perfect health, i.e. “no problem” answered for all dimensions of the questionnaire) to 0 (death), with negative values representing health states deemed worse than death [24]. Missing utilities were imputed using the mean of the patient’s treatment arm when both values were missing. When only one of the two values was missing, it was imputed using the existing value and the mean difference between baseline and 28 days in the patient’s treatment arm.

#### *2.4 Costs*

Healthcare resource consumption and costs were assessed using the SNIIRAM database. The analysis was carried out from the societal perspective in order to account for the impact of MS on patients’ capacity to work. Direct healthcare costs and indirect costs were included in the cost computation only if they were related to MS. Direct costs included hospitalizations, visits to a doctor (neurologist, general practitioner, ophthalmologist, other specialist) or to another healthcare professional (including physiotherapists and nurses), medications, medical devices, radiology and biological tests, and medical transport [25]. Indirect costs included sick-day leaves as it was the only information on productivity losses available. Missing cost data were imputed using the mean of patients’ treatment arm.

#### *2.5 Cost-utility analysis*

A cost-utility analysis was carried out to compare PO MP to IV MP at 28 days. In accordance with French guidelines, no discount rate was applied as the time horizon was too short.

An incremental cost-effectiveness ratio (ICER) was calculated by dividing the difference in mean costs between the two strategies by the difference in mean QALYs gained. This ICER represents the extra cost that must be spent to gain an additional QALY with the PO strategy. It was then placed on a cost-effectiveness plane to compare it to four possible outcomes: *i*) PO strategy is more effective and less costly and is therefore adopted; *ii*) PO strategy is less effective and more costly and is therefore

rejected; *iii*) PO strategy is more effective and more costly and it is up to decision-makers to decide whether they are willing to pay the extra cost; *iv*) PO strategy is less effective and also less costly, and decision-makers must then decide whether they are willing to part with some effectiveness to save costs.

To assess the uncertainty surrounding the results, we carried out a sensitivity analysis using bootstrapping methods and calculated new ICERs in 1,000 random resamples. They were then placed on a cost-effectiveness plane and used to build a cost-effectiveness acceptability curve, showing the probability that PO MP would be cost-effective for different willingness to pay by the decision-maker.

### *2.6 Scenario analysis*

As stated previously, PO MP was given to hospitalized patients during the COPOUSEP trial. In real-life conditions, it could be administered at home, as could IV MP. An alternative scenario analysis was therefore carried out to assess the cost-utility of at-home PO MP vs. at-home IV MP.

At-home treatment costs were calculated using established care protocols. They included visits to a medical doctor or to other healthcare professionals, medications, medical devices, and radiology and biological tests necessary for the treatment, with the addition of at-home nurse care in the IV arm.

Total costs at 28 days in real-life conditions were calculated by subtracting hospital and transport costs from the total costs in the COPOUSEP trial and adding the at-home costs.

### *2.7 Budgetary impact analysis*

The objective of a budgetary impact analysis is to assess the costs incurred (or saved) should a new strategy be generalized and become widely available to the eligible population. It compares two scenarios, the situation in which only IV MP is available to the French MS population and one in which PO MP becomes available as an alternative treatment option. The difference between the two is the budgetary impact of generalizing PO MP. As it made little sense to assess the budget impact of PO MP administered in hospital, the budgetary impact analysis assumed that both treatments could

be administered at home. It was carried out yearly over a five-year period in accordance with French guidelines [26].

The mean cost of a MS relapse was calculated at 90 days in the COPOUSEP population using the SNIIRAM database under the assumption that this time horizon would cover the duration of the potential consequences of the relapse (clinicians' opinion). Direct healthcare costs and indirect costs were included in the cost computation. The full method is presented in Appendix 1.

### *2.8 Statistical analysis*

Continuous variables were estimated in both treatment arms using mean and standard deviation (SD) and dichotomous variables using number and percentages. Comparisons between the two groups were carried out using a Mann-Whitney test for the former and a chi-2 test for the latter.

## **3. Results**

### *3.1 Population characteristics*

One hundred seventy-two patients from the per protocol population of the COPOUSEP trial had an assessable primary endpoint, i.e. 94.0% of the total per protocol population. Eighty-two were treated with PO MP and 90 with IV MP. Mean age was 34.6 years (SD=9.4) in the PO group vs. 35.8 (SD=9.9) in the IV group. There were respectively 73.2% and 77.8% of women in the two groups, and the median duration of MS was 7.2 (interquartile range=5.5) and 7.3 (interquartile range=5.7) years, respectively. Mean EDSS score at inclusion was 3.5 in both groups, secondary to the relapse [19].

### *3.2 Effectiveness*

Respectively seven (4.1%) and six (3.5%) patients in the PO and IV arm had missing utility data at baseline and 28 days, eight (4.7%) and two (1.2%) had missing data at baseline only, and eight (4.7%) and nine (5.2%) had missing data at 28 days only. At 28 days, patients' utility increased in both

groups and there was no significant difference between PO and IV patients in either utility or QALY gained (Table 1).

### *3.3 Costs*

Thirteen patients (7.6%) had missing cost data in the PO group vs. 21 (12.2%) in the IV group.

At 28 days and in the conditions of the trial (all patients treated at hospital) there was no significant difference in mean total costs per patient between the two groups (€2,012 vs. €1,981,  $p=0.5564$ ).

Acute hospital care amounted to the majority of the costs (79.2% of total costs), followed by sick leaves, medical transports and medications (Table 2).

In the alternative scenario analysis where treatment was administered at home, at-home treatment costs were calculated to be €167 for PO MP and €277 for IV MP, leading to a total cost at 28 days of €420 for PO MP and €578 for IV MP.

### *3.4 Cost-effectiveness analysis at 28 days*

In the conditions of the trial, the ICER was €15,360 per QALY gained. Bootstrap analyses found that there was an 80.0% chance that PO MP would increase health-related quality of life compared to IV MP and 35.6% chance that it would be more effective and less costly (Figure 1). In addition, if decision-makers were willing to spend €50,000 to gain an extra QALY, there would be a 64% chance that PO MP would be cost-effective, which rose to 74% for a willingness-to-pay of €100,000 (Figure 2).

In the alternative scenario analysis where treatment was administered at home, PO MP was more effective and less costly.

### *3.5 Budgetary impact analysis*

When at-home administration was considered, the cost-savings associated with making PO MP available could be as high as 25 million euros per year over a five-year period (see Appendix B for full details).

#### **4. Discussion**

This study is the first to assess the cost-utility of oral MP compared to IV MP in a randomized controlled trial. We found that oral MP was cost-effective even in the conditions of the trial for a threshold of €30,000 per QALY. When at-home treatment was an option, oral MP became both more effective and less costly than IV MP. In addition, the introduction of at-home oral MP at the national level would be associated with cost-savings of over 25 million euros annually.

There was little uncertainty surrounding our findings that oral MP is cost-effective, as shown by the sensitivity analyses. Because the economic evaluation was carried out alongside the clinical trial, there is also no uncertainty surrounding the relapse diagnosis, unlike other studies which had to use declarative data or algorithms to identify and classify relapses [27,28]. Through the use of a single national database, the SNIIRAM, we were able to identify with certainty all reimbursed care consumption by patients and not rely on declarative data or multiple sources.

Our estimated mean societal cost of a relapse in France (€3,767 including sick day leaves) is in line with previous publications. In 2016, Hawton and colleagues reported a mean cost of €4,295 at six months for relapses requiring a hospitalization in the UK [11]. In 2017, in a study including patients from 16 European countries, Kobelt and colleagues estimated the mean cost of relapse at three months to be €2,188, ranging from €632 to €4,569, with major variations depending on the severity of the disease [2].

The main limitation of our study arises from methodological reasons, the trial could not be performed at home and both IV and PO treatments were administered during a hospital stay, while in real life both can be administered at home or be initiated at the hospital and continued at home [18,29]. While there is no reason to believe that this has affected our effectiveness criteria, it

certainly had an important impact on costs. To overcome this limit, we calculated at-home treatment costs which may not be representative of all care experience in France. However, our estimated at-home IV treatment cost was close that found by a study in four French regions (€277 vs. €337) [29].

In addition, because the SNIRAM only collects reimbursed care, non-healthcare costs – in particular informal costs associated with carers – could not be considered. However, they are unlikely to differ between the two groups. Finally, the annual rate of relapses used in the budgetary impact analysis was a mean over a ten-year follow-up of newly diagnosed patients, while the literature reports higher relapse rates during the first five years which then tend to decrease and stabilize as time goes by. Cost-savings may therefore have been slightly overestimated.

Our findings entail a major evolution for the care of MS relapses. Indeed, while many studies have validated both the use of at-home IV MP to treat relapses and the protocols for how to do so [18,29], the benefits of PO MP in terms of cost-effectiveness and cost-savings should lead decision-makers to recommend its use at a time when most healthcare systems face increasing budget constraints and must make decisions on resource allocation. Clinicians too should prioritize this type of treatment whenever possible for the majority of MS relapses, relying on validated protocols involving general practitioners. While our study was set in France, we believe its results are generalizable to all healthcare systems as it seems highly unlikely that a PO treatment would be more costly than an IV one in any type of setting.

Beyond the cost-effectiveness and cost-saving aspects, PO treatment for MS relapses could also have a major impact on patients: the ease and autonomy that PO treatment offers should lead to prolonged improved quality of life and a further increase in patient satisfaction, already evidenced in at-home IV treatment [18,29]. Some may also choose to go to work while on PO treatment, which will lead to further productivity gains.

However, at-home PO treatment of MS relapses could also be associated with vast changes for neurology departments. Outpatient treatment of MS relapses currently represents an important part of their activity. A decrease in those admissions could modify the profile of admitted patients and

therefore have a significant impact on the work of healthcare professionals. These changes could also represent an opportunity to develop outpatient management of patients suffering from other chronic neurological diseases.

Decision-makers, clinicians, and patients should therefore strive to find a way to implement these new practices in order to meet patients' expectations and increase the efficiency of the healthcare system. Further qualitative work may be needed to assess how to implement these changes into clinical practice under the best conditions.

### **Conclusion**

For several years, neurology teams have considered that at-home treatment of MS relapses should be encouraged whenever possible as it improves both patients' quality of life and satisfaction. This new evidence based on a randomized double-blind controlled trial and exhaustive healthcare consumption data should facilitate its dissemination thanks to the ease of the PO use, which was already found to be non-inferior to IV MP in terms of efficacy and has now been shown to be cost-effective as well. Prescribing PO MP for MS relapses should further increase patient satisfaction and decrease the economic burden MS places on healthcare systems.

### **Funding**

This study was funded by the French Health Ministry, the *Ligue Française contre la SEP*, and Teva. The funders had no role in the design and conduct of the study; data collection, management, analysis, or interpretation; preparation, review, or approval of the manuscript; decision to submit the manuscript for publication.

### **Competing interest**

DV and RW received grants from the French Health Ministry, the *Ligue Française contre la SEP* and TEVA during the conduct of the study. ELP reports personal fees from Biogen, Roche, Merck,

Novartis, Sanofi-Genzyme outside the submitted work. GE reports research grants from Merck, Biogen, Teva Pharma, Novartis, Roche and Sanofi, and personal fees from Biogenidec, Sanofi and Novartis outside the submitted work. DL reports personal fees from Biogen, Merck and Novartis, grants and personal fees from Roche, MedDay and Sanofi-Genzyme, and grants from Fondation ARSEP, outside the submitted work. FZ, MC, SW, CL, MM and KC have nothing to disclose.

### **Author contributions**

MM participated in designing the economic evaluation, carried out the economic analyses and interpretation of data, drafted the initial manuscript, and reviewed and revised the manuscript.

KC played a major role in conceptualizing and designing the economic study, supervised the economic analysis, interpreted the data, and reviewed and revised the manuscript.

DV participated in the literature search, conception, study design, statistical analysis, data interpretation, and manuscript writing of COPOUSEP trial. He participated in the literature search, and designing the economic evaluation, in interpretation of data and reviewed and revised the manuscript submitted.

ELP performed the literature search, participated to conception, study design, statistical analysis, data interpretation, and wrote the manuscript of COPOUSEP trial. She also participated in interpretation of data and reviewed and revised the manuscript submitted for the economy study.

GE participated in enrolment of patients, data gathering, analysis, and interpretation, and revision of the report. He also revised the manuscript submitted for the economy study.

DL, RW, CL, FZ, SW, VD, and MC participated in enrolment of patients, data interpretation, and writing the manuscript for the COPOUSEP trial.

All authors have approved the final version of the manuscript and its submission.



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**Table 1. Mean utilities and quality-adjusted life-year associated with oral and intravenous methylprednisolone at 28 days**

	PO MP	IV MP	Difference (95%CI)	p
Mean utility at baseline (SD)	0.671 (0.239)	0.611 (0.248)	0.060 (-0.13 – 0.133)	0.1049
Mean utility at 28 days (SD)	0.736 (0.210)	0.740 (0.252)	-0.004 (-0.074 – 0.066)	0.5407
Mean evolution between (SD) baseline and 28 days (SD)	0.064 (0.207)	0.130 (0.241)	-0.066 (-0.133 – 0.001)	0.0766
Mean QALY at 28 days (SD)	0.054 (0.016)	0.052 (0.017)	0.002 (-0.003 – 0.007)	0.6221

IV: intravenous; PO: per os; MP: methylprednisolone; 95%CI: 95% confidence interval; SD: standard deviation; QALY: quality-adjusted life-year

**Table 2. Mean costs associated with intravenous (IV) and oral (PO) methylprednisolone (MP) at 28 days in the conditions of the COPOUSEP trial, in euros**

	PO MP	IV MP	Difference (95%CI)	p
	Mean (SD)	Mean (SD)		
Acute hospital care	1,543 (445)	1,569 (695)	-26 (-203 – 150)	0.6479
Rehabilitation hospital care	89 (680)	0 (0)	89 (-51 – 230)	<0.0001
Doctor visits	21 (26)	18 (22)	3 (-4 – 10)	0.8113
Other healthcare professional visits	8 (22)	11 (31)	-3 (-12 – 5)	0.0437
Medications	65 (244)	122 (302)	-57 (-139 – 26)	0.1305
Medical devices	6 (31)	5 (30)	1 (-8 – 10)	0.8007
Radiology & biological tests	20 (100)	7 (18)	13 (-8 – 34)	0.8578
Transports	127 (441)	110 (349)	17 (-102 – 135)	0.3899
Total direct healthcare costs	1,879 (1,049)	1,843 (881)	36 (-253 – 324)	0.6769
Sick leaves	133 (382)	138 (276)	-5 (-104 – 94)	0.2357
Total costs	2,012 (1,113)	1,981 (1,010)	31 (-287 – 348)	0.5564

IV: intra-venous; PO: per os; MP: methylprednisolone; 95%CI: 95% confidence interval; SD: standard deviation

**Figure 1. Sensitivity analysis of the cost-utility analysis at 28 days using bootstrap methods**

X axis: Effectiveness difference, in quality-adjusted life-years

Y axis: Cost difference, in euros

**Figure 2. Cost-effectiveness acceptability curve**

X axis: Willingness to pay for an additional quality-adjusted life-year, in euros

Y axis: Probability that oral methylprednisolone would be cost-effective



Figure 1

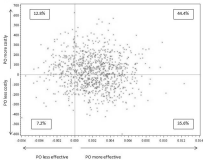


Figure 2

