

# Anti-IL-4R versus Anti-IL-5/5R after Anti-IL-5/5R failure in asthma: an emulated target trial

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## **Keywords:**

MeSH; benralizumab; dupilumab; mepolizumab; severe asthma; treatment switch.

## **Abbreviations used**

ACT: Asthma Control Test

AQLQ: Asthma Quality of Life Questionnaire

BEC: Blood eosinophil count

CRwNP: Chronic rhinosinusitis with nasal polyps

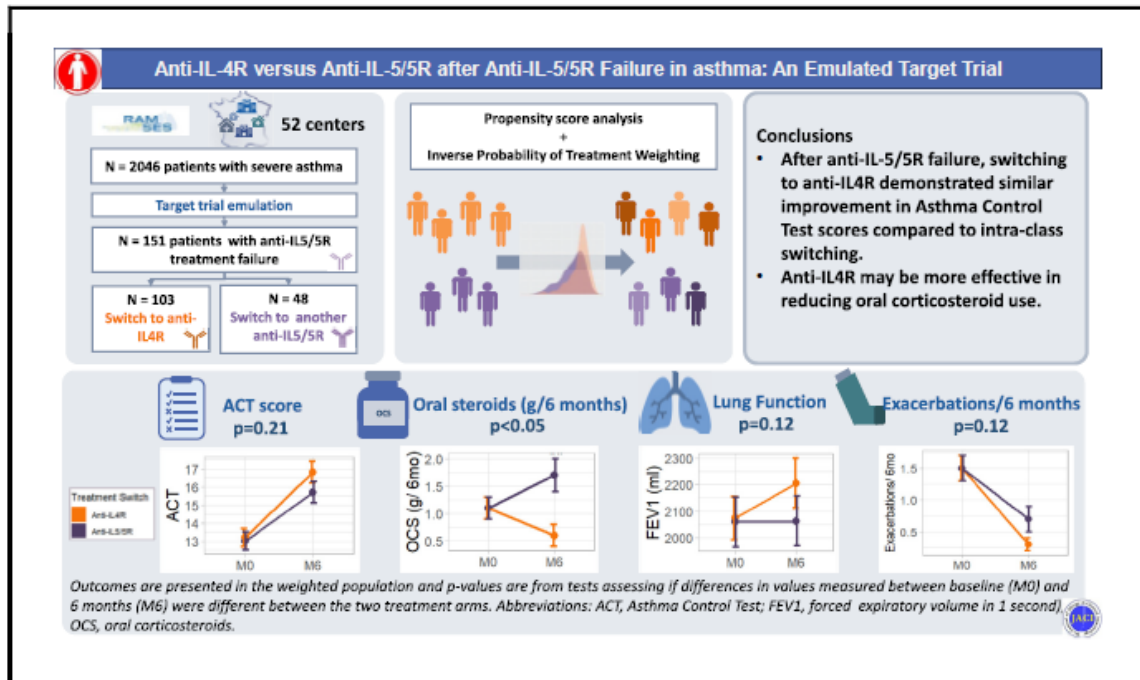
OCS: Oral corticosteroid

OR: Odds ratio

RAMSES: Recherche sur les AsthMes SEvèreS

SA: Severe asthma

## GRAPHICAL ABSTRACT



**Capsule summary:** In this target trial emulation, in patients with severe asthma with insufficient response to a first anti-IL-5/5R, switching to dupilumab was associated with similar improvement in Asthma Control Test score as switching to anti-IL-5/5R mAb but appeared more effective for oral corticosteroid reduction.

## Abstract

### Background:

Switching biologics is now common practice in severe eosinophilic asthma. After insufficient response to anti-interleukin 5 or 5 receptor (anti-IL-5/5R), the optimal switch between an anti-IL-4R monoclonal antibody (mAb) (inter-class) or another anti-IL-5/5R drug (intra-class) remains unknown.

### Objective:

We compared the effectiveness of these two strategies on asthma control in patients with severe eosinophilic asthma and insufficient response to an anti-IL-5/5R mAb.

### Methods:

We emulated a target randomized trial using observational data from the RAMSES Cohort. Eligible patients were switched to an anti-IL-4R mAb or another anti-IL-5/5R drug after insufficient response to an anti-IL-5/5R mAb. The primary outcome was the change in Asthma Control Test (ACT) score at 6 months.

### Results:

Among the 2046 patients in the cohort, 151 were included in the study: 103 switched to an anti-IL-4R mAb and 48 to another anti-IL-5/5R. At 6 months, the difference in ACT score

improvement was not statistically significant (mean difference groups, 0.82 [-0.47 to 2.10],  $p=0.213$ ). The inter-class group exhibited greater cumulative reduction in oral corticosteroids dose ( $P_{\text{inter-intra}}$  -1.05g [-1.76 to -0.34],  $p=0.041$ ). The inter-class group had a better effect, although not significantly, on reducing exacerbations ( $\Delta_{\text{inter-intra}}$  -0.37 [-0.77 to 0.02],  $p=0.124$ ) and increasing lung function (FEV1) (126.8 ml [-12.7 to 266.4],  $p=0.124$ ).

### **Conclusion:**

After anti-IL-5/5R mAb insufficient response, switching to dupilumab demonstrated similar improvement in ACT scores compared to intra-class switching. However, it appeared more effective in reducing oral corticosteroid use. Larger studies are warranted to confirm these results.

Biologics have greatly modified the management of severe asthma (SA) for the last 2 decades. In phase III clinical trials, they demonstrated efficacy on exacerbations and reducing oral corticosteroid (OCS) consumption, asthma control, and quality of life.<sup>1-4</sup> However, the clinical response varies among individuals: depending on the definition, about 70% of people with asthma are considered responders, 10% to 20% are “super responders,” and the remainder have intermediate or poor response.<sup>5-9</sup> Therefore, for these latter individuals, a switch to another drug is possible because the drugs target similar patients with SA and type 2 inflammation.

In real life, switches occur for 11% to 41% of patients,<sup>5,10-12</sup> mainly because of insufficient efficacy, but the optimal switching strategies have not been identified. With failure of an anti-IL-5 or anti-IL-5R mAb, 2 main strategies were used in France for eosinophilic patients before tezepelumab was available: switching to dupilumab (anti-IL-4R) or to another anti-IL-5/5R mAb because the indications are similar. In small retrospective series, switching from an anti-IL-5/5R mAb to dupilumab was associated with improved asthma control and lung function.<sup>10,13,14</sup> The same outcomes were reported after a switch within anti-IL-5/5R drugs.<sup>11,15</sup>

To our knowledge, these 2 switching strategies have not been directly compared. This study compared the effectiveness of the 2 switching strategies in asthma control in severe eosinophilic asthma patients with insufficient response to a first anti-IL-5/5R mAb.

## METHODS

### Study design

Using data for patients with SA included in the RAMSES (Recherche sur les AsthMes SEvères) cohort, we emulated a target trial of patients with insufficient response to an anti-IL-5/5R mAb to compare switching to dupilumab (anti-IL-4R, interclass switch) and switching within the same therapeutic class (ie, switch from benralizumab to mepolizumab or switch from mepolizumab to benralizumab; intraclass switch). The reporting of this study complies with the Strengthening the reporting of observational studies in epidemiology (STROBE) statement<sup>16</sup> (see [Table E1](#) in this article’s Online Repository at [www.jacionline.org](http://www.jacionline.org)).

### Study population and data collection

The French respiratory diseases society initiated the RAMSES cohort to evaluate the effectiveness and safety of biologics in patients with SA in France.<sup>17</sup> The RAMSES cohort eligibility criteria are available in [Table E2](#) (in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)). SA was defined following the American Thoracic Society/European Respiratory Society guidelines definition.<sup>18</sup>

The RAMSES cohort prospectively included 2046 adults with SA from September 2019 to September 2022 across 52 centers in France. Patients were evaluated at inclusion and then every 6 months for 5 years. Patient care and choices of treatment were not influenced by their participation in RAMSES and therefore reflect real-life practices.

The RAMSES cohort received approval from the ethical committee in France (CPP Sud-Est IV, ID-RCB: 2018-A03282-53) and was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT04077528). According to French legislation, patients were informed of the study and did not object to their inclusion in the cohort. The present target trial emulation was registered in the European Union electronic Register of Post-Authorization Studies Register (EUPAS105374).

### **Eligibility criteria**

The first step of our emulated target trial was to specify the key protocol components of the target trial, or the theoretical randomized trial that would have been undertaken to answer our research question, and then to emulate all these components in the observational setting.<sup>12</sup> The protocol components of the target trial and its emulation are available in [Table E3](#) (in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)).

Eligible participants received a first line of mepolizumab or benralizumab (reslizumab is not reimbursed in France), which was stopped because of failure or insufficient response.<sup>19</sup> In the observational emulation, treatment failures were identified on the basis of routine care assessments by physicians. This information was recorded in the electronic Case Report Form for the RAMSES cohort, specifically under the category “Reason for discontinuation.” Therefore, we included in the analysis only those patients who discontinued treatment because of failure or insufficient response. Patients who had already received anti-IL-4/4R or the 2 anti-IL-5/5R drugs were excluded because they were not eligible for both evaluated strategies. Only treatment with omalizumab before the anti-IL-5/5R line was allowed. The second biologic had to be initiated less than 6 months after the anti-IL-5/5R discontinuation, and potential follow-up in the cohort after switches had to be at least 6 months to allow for a minimum “look-back” period of 6 months ([Fig 1](#)).

Treatment strategies and treatment assignment After failure of a first anti-IL-5/5R mAb, the 2 treatment strategies of interest were (1) switching within the same therapeutic class (intra-class switch) and (2) switching to dupilumab (interclass switch). Special attention was paid to ensure the alignment of the times of eligibility assessment, treatment assignment, and start of follow-up (treatment switch), to avoid introducing biases in the analysis<sup>20</sup> ([Fig 1](#)).

### **Outcomes**

Our primary outcome was the change in Asthma Control Test (ACT) score 6 months after the switch. ACT belongs to the core outcome set for evaluation of treatments in SA and, as a patient reported outcome, is highly relevant for them.<sup>21</sup> In addition, the assessment of asthma control using scores centered on symptoms is a key component in evaluating the clinical response to biologics in real-life conditions.<sup>22,23</sup> Secondary outcomes were change in exacerbation rate between the 6 months before enrollment and the 6-month follow-up period (exacerbation was defined as worsening asthma symptoms requiring a systemic corticosteroid course or doubling the daily maintenance dose for at least 48 hours, and severe exacerbation as an emergency department visit or hospitalization); change in cumulative OCS dose between the 6 months before the switch and the 6-month follow-up period (including maintenance OCS and exacerbation courses); change in FEV1; change in Asthma Quality of Life Questionnaire (AQLQ) score; and number of patients with ACT score of 20 or more, change in ACT score of 3 or more points, 50% reduction in exacerbations, 50% reduction in OCS intake, and discontinuation of treatment, all at 6 months after the switch.

All continuous outcomes were the differences in values measured at 6 months and at baseline and are presented as the difference in differences between the intraclass and interclass groups in results. [Fig 1](#) presents the time frames when data collection for covariates and outcomes was permitted.

## Statistical analysis

We balanced characteristics of patients at baseline (time of switch) using a propensity score.<sup>24</sup> On the basis of literature and expert knowledge, we drew a directed acyclic graph using DAGitty software (see [Fig E1](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).<sup>25,26</sup> The identified key confounders were age, sex, body mass index, absolute FEV1, OCS cumulative dose, atopy (positive prick test result and/or specific IgE > 0.35 KU/L for >1 common aeroallergen), blood eosinophil count (BEC), history of chronic rhinosinusitis with nasal polyps, exacerbation rate in the previous 6 months, and ACT score, all measured at baseline. History of atopic dermatitis was not included because no patient in our sample reported it. Previous use of omalizumab was also not included because of its high correlation with the atopy covariate. The probability of receiving the interclass strategy (ie, propensity score) was modeled with a multivariable logistic regression model that included all the selected key confounders. We then used a linear regression model, with a strategy of inverse probability of treatment weighting, to estimate the average treatment effect of the switching strategies on ACT score improvement at 6 months.<sup>24</sup> Weights were truncated to the 1st and 99th percentiles. Patient characteristics are described overall and by treatment strategy for the unweighted and weighted populations. Quantitative variables are described with means (SD) and categorical variables with numbers (percentage). The positivity assumption for the propensity score analysis was checked by plotting the propensity score distribution for each group (see [Fig E2](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). We assessed balanced characteristics before and after weighting with absolute standard mean differences ([Table I](#); see [Fig E3](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

Effects on secondary outcomes were estimated with logistic regressions for binary variables and linear regressions for continuous variables. All treatment effects were estimated for an observational analog of an intention-to-treat population (ie, patients who received a prescription of the switching strategy at baseline). As part of post hoc analyses, paired t tests were conducted for each group within the unweighted population (eg, in the intraclass group, n 5 48, and in the interclass group, n 5 103) to evaluate whether asthma was alleviated after the switch.

## Missing data

Multiple imputations using chained equations were used to handle missing data on covariates and outcomes, assuming that data were missing at random.<sup>27</sup> No data were missing for treatment strategy exposure. ACT, FEV1, and AQLQ score were imputed at baseline and at the end point; body mass index and BEC were imputed at baseline only. The covariates with the highest rates of missingness were FEV1 (30.5% at baseline) and the AQLQ score (26.5% at baseline) ([Table I](#); see [Table E4](#) in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)). Missing data were imputed 50 times. The propensity score was estimated on each imputed data set; the treatment effects were estimated for the weighted population and then pooled according to Rubin's rule.<sup>28</sup>

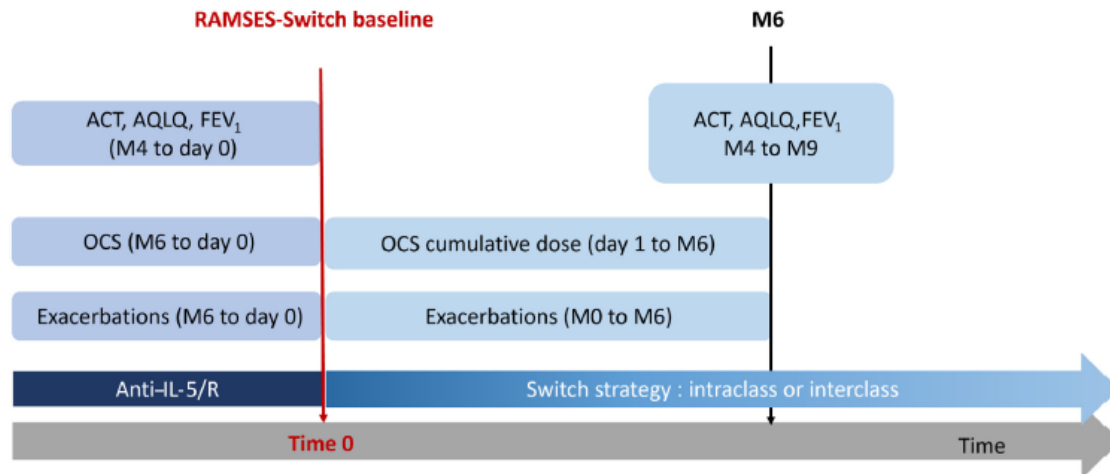


FIG 1. RAMSES-Switch study design. FVC, Forced vital capacity; IL, interleukin; M, month.

TABLE I. Patient characteristics for the baseline unweighted population and propensity-weighted population

Characteristic	Missing values, n (%)	Unweighted population			ASMD	Propensity-weighted population		
		All (n = 151)	Interclass strategy (n = 103)	Intraclass strategy (n = 48)		Interclass strategy	Intraclass strategy	ASMD
Age (y)	0 (0)	52.0 (14.6)	52.1 (14.8)	50.4 (14.1)	0.122	51.5 (1.6)	52.1 (1.5)	0.016
Sex: female	0 (0)	94 (62.3)	65 (63.1)	29 (60.4)	0.055	63.3%	57.2%	0.016
BMI (kg/m <sup>2</sup> )	1 (0.7)	27.4 (5.1)	27.5 (5.2)	27.3 (4.9)	0.182	27.6 (0.5)	27.5 (0.4)	0.003
Smoking history*	—	63 (41.7)	40 (38.8)	23 (47.9)	0.112	39.3%	47.5%	0.061
Duration of asthma (y)	8 (5.3)	21.0 (16.0)	21.6 (16.7)	19.6 (14.3)	0.127	21.2 (1.6)	19.7 (2.1)	0.042
Duration of SA (y)	14 (9.3)	10.0 (9.2)	9.4 (8.8)	11.3 (10.0)	0.205	11.5 (0.9)	9.1 (1.6)	0.091
BEC (mm <sup>3</sup> )†	14 (9.3)	242 (382)	263 (430)	196 (243)	0.188	240 (32.3)	216 (30.6)	0.024
Atopy‡	0 (0)	58 (38.4)	39 (37.9)	19 (39.6)	0.035	40.1%	38.2%	<0.001
Chronic rhinosinusitis	0 (0)	61 (40.4)	37 (35.9)	24 (50.0)	0.259	36.7%	47.5%	0.095
CRwNP	0 (0)	50 (33.1)	36 (35.0)	14 (29.2)	0.123	32.8%	29.9%	0.003
Nasal surgery	0 (0)	34 (22.5)	26 (25.2)	10 (20.8)	0.156	17.0%	23.8%	0.018
FEV <sub>1</sub> (mL)	46 (30.5)	2076 (864)	2041 (861)	2154 (879)	<0.001	2074 (81)	2059 (94)	0.004
FEV <sub>1</sub> (%)	46 (30.5)	71.6 (22.5)	70.9 (21.8)	73.1 (24.2)	0.095	70.0 (2.3)	72.6 (3.9)	0.032
FVC (%)	47 (31.1)	95.5 (40.0)	92.4 (20.7)	102.4 (64.8)	0.209	91.1 (2.3)	117.5 (16.4)	0.072
Cumulative OCS dose (g, equivalent prednisolone)§	0 (0)	1.0 (1.9)	0.8 (1.7)	1.4 (2.4)	0.316	1.1 (0.2)	1.1 (0.2)	0.010
Exacerbations count§	0 (0)	1.4 (1.8)	1.2 (1.6)	2.0 (2.1)	0.434	1.5 (0.2)	1.5 (0.2)	0.005
Severe exacerbations count§	0 (0)	0.2 (0.8)	0.3 (0.90)	0.2 (0.7)	0.028	0.2 (0.1)	0.2 (0.1)	0.007
Mepolizumab before switch	0 (0)	111 (73.5)	70 (68.0)	41 (85.4)	0.419	68.4%	83.6%	0.234
Benralizumab before switch	0 (0)	40 (26.4)	33 (32.0)	7 (14.6)	—	31.6%	16.4%	—
Duration of anti-IL-5/5R treatment before switch (d)	0 (0)	682 (483)	709 (479)	624 (489)	0.176	675 (43.5)	667 (79.2)	0.004
Time from last anti-IL-5/5R injection and first switch treatment injection (d)	0 (0)	22.7 (37.1)	20.0 (35.3)	28.5 (40.5)	0.223	21.33 (4.9)	27.5 (5.9)	0.066
Baseline ACT score	29 (19.2)	13.4 (5.5)	14.0 (5.8)	12.1 (4.6)	0.313	13.2 (0.5)	13.0 (0.5)	0.007
Baseline AQLQ score	40 (26.5)	4.5 (1.2)	4.6 (1.2)	4.2 (1.1)	0.257	4.5 (0.1)	4.4 (0.1)	0.014
Baseline SNOT-22 score	79 (52.3)	49.5 (20.3)	51.5 (21.8)	45.1 (16.2)	0.331	51.5 (3.0)	45.9 (3.7)	0.099

Data are n (%) or mean (SD), unless otherwise specified. SEs were estimated by bootstrap.

The populations are described for the imputed data sets.

ASMD, Absolute standardized mean difference; BMI, body mass index; FVC, forced vital capacity; SNOT-22, Sino-Nasal Outcome Test.

\*Defined ex-smokers (n = 56) and current smokers (n = 7).

†BEC nearest to time of switch (always pre-switch).

‡Defined as positive prick test result and/or specific IgE for ≥1 common aeroallergen.

§Over the 6 mo before enrollment in RAMSES-Switch.

## Subgroup analysis

We performed 5 subgroup analyses for the primary outcome (the first 2 were planned and the last 3 were added on post hoc analyses), introducing a term of interaction in the linear regressions according to (1) the history of chronic rhinosinusitis, (2) the anti-IL-5/5R mAb received before the switch, (3) the baseline BEC, (4) the atopic status, and (5) the nasal polyposis status.



## Sensitivity analyses

We performed 2 sensitivity analyses: (1) ACT score at 6 months adjusted on the baseline ACT score instead of the change in the ACT score from baseline to 6 months and (2) analysis weighted to estimate the average treatment effect on the treated. We planned but did not perform an analysis restricted to switches after 2020 (dupilumab availability in France) because only 1 patient switched before 2020.

P less than .05 was considered statistically significant. We corrected for multiple comparisons on secondary outcomes by using the Benjamini-Hochberg procedure for treatment effect estimates in the weighted population. Nonetheless, these analyses remain exploratory. Robust variances were estimated by bootstrap (2000 iterations) and then used to compute 95% CIs of treatment effect measures. Statistical analyses were performed with R v4.2.3 (The R Foundation for Statistical Computing, Vienna, Austria).<sup>29</sup>

## RESULTS

### Population

At the time of database lock on May 24, 2023, 151 patients of the RAMSES cohort met eligibility criteria for the RAMSES-Switch study: 103 in the interclass strategy group and 48 in the intraclass strategy group (Fig 2). Table I outlines participant characteristics at baseline. Overall, 41 (85.4%) participants in the intraclass group and 70 (68%) in the interclass group were on mepolizumab before the switch. In the unweighted population, 94 patients were females (62%), the mean age was 52 +/- 14.6 years, and mean body mass index was 27.1 +/- 5.1 kg/m<sup>2</sup>. Overall, 55 patients (33.1%) had chronic rhinosinusitis with nasal polyps (CRwNP). The mean BEC was 242/mm<sup>3</sup> +/- 382/mm<sup>3</sup>, and the mean cumulative OCS dose over 6 months before the switch was 1.0 +/- 1.9 g equivalent prednisolone. The mean exacerbation rate over the previous 6 months before the switch was 1.4 +/- 1.8. Participants received anti-IL-5/5R for a mean of 682 +/- 483 days before the switch. Switches were performed at a mean of 22.7 +/- 37.1 days after the last injection. After weighting, most patient characteristics were well balanced between the treatment strategy groups (absolute standard mean difference < 0.10).

### Primary outcome

In the unweighted population, the 6-month ACT score significantly improved after the switch in both strategy groups (mean ACT score change: interclass group, 3.37 [95% CI, 3.26 to 3.48], P <.001; intraclass group, 2.94 [95% CI, 2.73 to 3.15], P=.002). In the weighted analysis, after 6 months of follow-up, the ACT score improved from 13.0 (0.5) to 15.7 (0.6) in the intraclass group and from 13.2 (0.5) to 16.8 (0.6) in the interclass group. After propensity score weighting to estimate the average treatment effect, the mean difference between intraclass and interclass groups ( $\Delta_{\text{inter-intra}}$ ) was 0.82 (95% CI, 0.47 to 1.10), in favor of the interclass strategy (P =.213) (Table II and Fig 3; see Table E4).

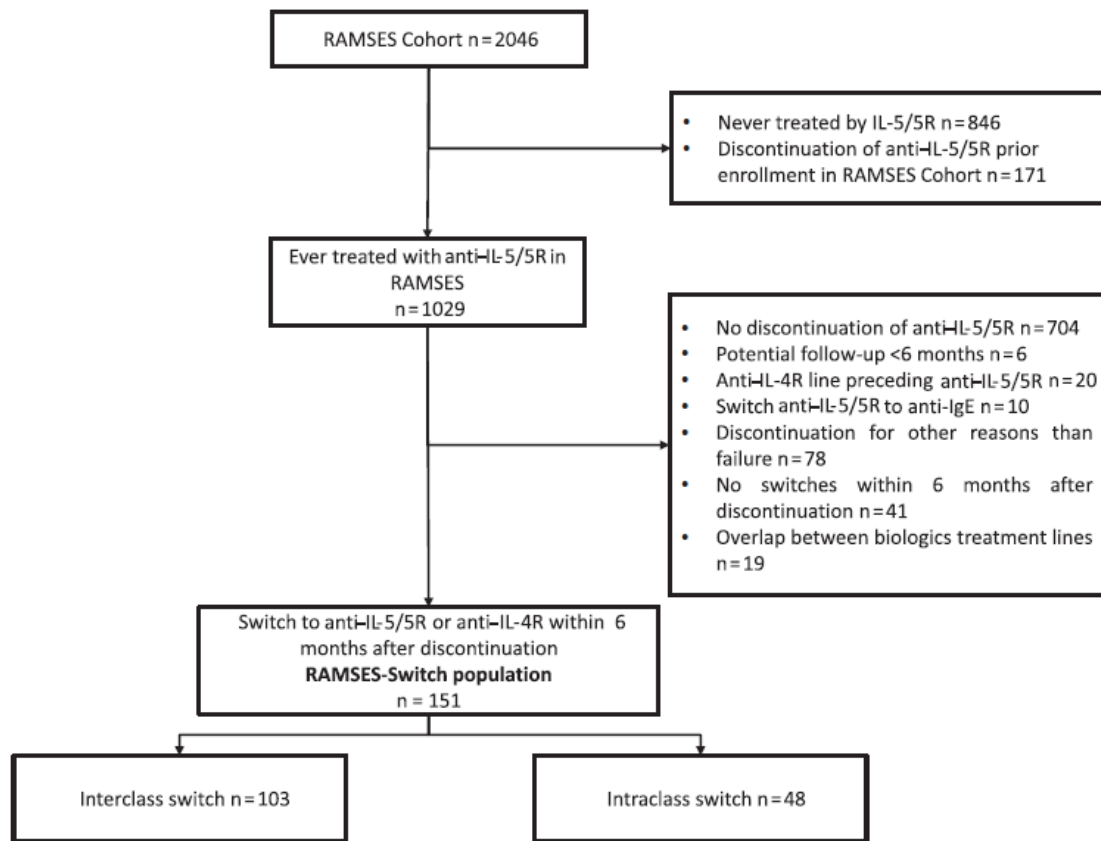


FIG 2. Study flowchart.

## Secondary outcomes

In the unweighted population, the OCS cumulative dose decreased by 0.19 g (95% CI, 20.21 to 20.16;  $P = .205$ ) in the interclass group and increased by 0.43 g (95% CI, 0.33 to 0.52;  $P = .185$ ) in the intraclass group; for both groups, statistical significance was not reached. Exacerbation rate decreased by 0.86 (95% CI, 20.89 to 20.84;  $P < .001$ ) in the interclass group and by 1.17 (95% CI, 21.28 to 21.06;  $P < .001$ ) in the intraclass group. FEV1 increased by 134.6 mL over the 6-month period (95% CI, 123.4 to 145.8;  $P = .106$ ) in the interclass group and by 10.7 mL (95% CI, 211.9 to 33.3;  $P = .967$ ) in the intraclass group. Finally, in both groups, the AQLQ score significantly improved after 6 months by 0.53 point (95% CI, 0.51 to 0.55;  $P = .001$ ) in the interclass group and by 0.52 point (95% CI, 0.49 to 0.55;  $P = .011$ ) in the intraclass group (Table II; see Table E4).

In the weighted analysis, the reduction in cumulative OCS dose at 6 months was greater in the interclass group than in the intraclass group ( $\Delta_{\text{inter-intra}}$ , - 1.05 g; 95% CI, - 1.76 to - 0.34;  $P = .041$ ) (Fig 3).

The change in exacerbation rate did not significantly differ between groups but favored the interclass group ( $\Delta_{\text{inter-intra}}$  - 0.37; 95% CI, - 0.77 to 0.02;  $P = .124$ ). The groups did not differ in change in severe exacerbations ( $\Delta_{\text{inter-intra}}$ , - 0.09; 95% CI, - 0.27 to 0.08;  $P = .407$ ). The odds ratio (OR) for reducing by 50% the OCS dose and for reducing by 50% the exacerbation rate over the 6-month follow-up both favored the interclass group although not significantly (OR, 2.48, 95% CI, 1.18 to 5.21,  $P = .068$ , and OR, 3.08, 95% CI, 1.18 to 7.97,  $P = .068$ ).

Between baseline and 6 months, the FEV1 increase was higher (but not significantly) in the interclass group than in the intraclass group ( $\Delta_{\text{inter-intra}}$  126.8 mL; 95% CI, - 12.7 to 266.4;  $P = .124$ ). The 2 strategy groups did not differ in the AQLQ score improvement after 6 months ( $\Delta_{\text{inter-intra}}$ , - 0.02; 95% CI, - 0.31 to 0.26;  $P = .867$ ).

TABLE II. Primary and secondary outcomes at 6 mo after switch

Outcomes	Missing values, n (%)	Outcomes in the unweighted population		Unweighted analysis		Weighted analysis ATE		Adjusted P values <sup>‡</sup>
		Interclass strategy (n = 103)	Intraclass strategy (n = 48)	Effect measure* <sup>†</sup>	P value	Effect measure* <sup>†</sup>	P value	
<b>Primary outcome<sup>§</sup></b>								
Difference in mean improved ACT score	44 (29.1)	3.37 (0.60)	2.94 (0.72)	0.43 (-1.15 to 2.01)	.591	0.82 (-0.47 to 2.10)	.213	
<b>Secondary outcomes<sup>§</sup></b>								
Difference in reduced exacerbations count	0 (0)	-0.86 (0.16)	-1.17 (0.27)	0.31 (-0.30 to 0.93)	.315	-0.37 (-0.77 to 0.02)	.064	.124
Difference in reduced severe exacerbations count	0 (0)	-0.15 (0.06)	-0.02 (0.1)	-0.13 (-0.37 to 0.10)	.251	-0.09 (-0.27 to 0.08)	.285	.407
Difference in improved AQLQ score	54 (35.7)	0.53 (0.13)	0.52 (0.14)	0.01 (-0.29 to 0.30)	.966	-0.02 (-0.31 to 0.26)	.867	.867
Difference in absolute change in FEV <sub>1</sub> (mL)	66 (43.7)	134.6 (73.1)	10.7 (80.2)	123.9 (-9.9 to 257.7)	.069	126.8 (-12.7 to 266.4)	.074	.124
Difference in cumulative OCS dose (g, prednisolone)	0 (0)	-0.19 (0.15)	0.43 (0.33)	-0.62 (-1.33 to 0.09)	.085	-1.05 (-1.76 to -0.34)	.004	.041
Patients with ACT score $\geq 20$	44 (29.1)	43.3	22.5	2.73 (1.32 to 5.67)	.007	2.00 (1.01 to 3.96)	.046	.112
Patients with improved ACT score $\geq 3$ points	44 (29.1)	50.9	54.2	0.87 (0.47 to 1.61)	.661	0.93 (0.50 to 1.75)	.831	.867
Proportion of patients with 50% reduced exacerbations count	0 (0)	87.4%	70.9%	2.88 (1.14 to 7.28)	.025	3.08 (1.18 to 7.97)	.020	.068
Proportion of patients with 50% reduced cumulative OCS dose	0 (0)	74.9%	52.0%	2.78 (1.30 to 5.90)	.008	2.48 (1.18 to 5.21)	.017	.068
Proportion of patients discontinuing treatment before 6 mo <sup>  </sup>	0 (0)	16.4%	7.7%	1.34 (0.65 to 2.77)	.417	1.25 (0.57 to 2.77)	.574	.718

Data are n (%) or mean (SD), unless otherwise specified.

ATE, Average treatment effect; FVC, forced vital capacity.

\*Estimates are presented with their corresponding 95% CIs.

<sup>†</sup>SEs were estimated by bootstrap.

<sup>‡</sup>P values for secondary outcomes were adjusted for multiples comparisons by using the Benjamini-Hochberg procedure (false-discovery rate 5%).

<sup>§</sup>Estimates are mean difference in differences, comparing the interclass strategy with the intraclass strategy, or OR.

<sup>||</sup>In the interclass group, 4 over 8 patients discontinued the treatment because of an adverse event and the remaining 4 because of treatment failure. In the intraclass group, all discontinuations except 1 were due to treatment failure, with the remaining patient having an adverse event.

The interclass switch was associated, although not significantly, with a higher proportion of patients reaching an ACT score of 20 or more (OR, 2.00; 95% CI, 1.01 to 3.96;  $P = .115$ ). The 2 strategy groups did not differ in the proportion of patients achieving a 3-point improvement in the ACT score at 6 months (OR, 0.93; 95% CI, 0.50 to 1.75;  $P = .867$ ).

The groups did not differ in treatment discontinuation at 6 months (OR, 1.25; 95% CI, 0.57 to 2.77;  $P = .718$ ) (Table II).

### Subgroup analyses

In total, 111 patients (73.5%) received mepolizumab, 40 (26.4%) benralizumab before enrollment, 61 (40.3%) had a history of chronic rhinosinusitis, 99 (65.6%) had BEC more than 300/mm<sup>3</sup>, 58 (38.4%) had atopy, and 36 (35%) had CRwNP. No subgroup seemed to benefit more from 1 of the 2 strategies in terms of the ACT score change at 6 months (Fig 4; see Table E5 in this article's Online Repository at [www.jacionline.org](http://www.jacionline.org)).

## Sensitivity analyses

Sensitivity analyses (the ACT score at 6 months adjusted on the baseline ACT score; estimation of average treatment effect on the treated, and imputation of data by the median) were consistent with the main analysis. Further information can be found in Table E6 (in the Online Repository available at [www.jacionline.org](http://www.jacionline.org)).

## DISCUSSION

In this emulated target trial, we performed the first real-life direct comparison between 2 switching strategies after insufficient response to first anti-IL-5/5R treatment in patients with severe eosinophilic asthma. The improvement in the ACT score at 6 months did not differ between the 2 strategies. The OCS intake was significantly lower in the interclass group than in the intraclass group at 6 months. Changes in exacerbation rate and FEV<sub>1</sub> also favored the switch to dupilumab, although not significantly. Furthermore, several findings are consistent with a possible superiority of the switch strategy to dupilumab over the intraclass switch: an increased proportion of patients with an ACT score of 20 or more at 6 months and an increased proportion of patients with a 50% reduction in exacerbation rate and OCS intake, although these findings were not significant.

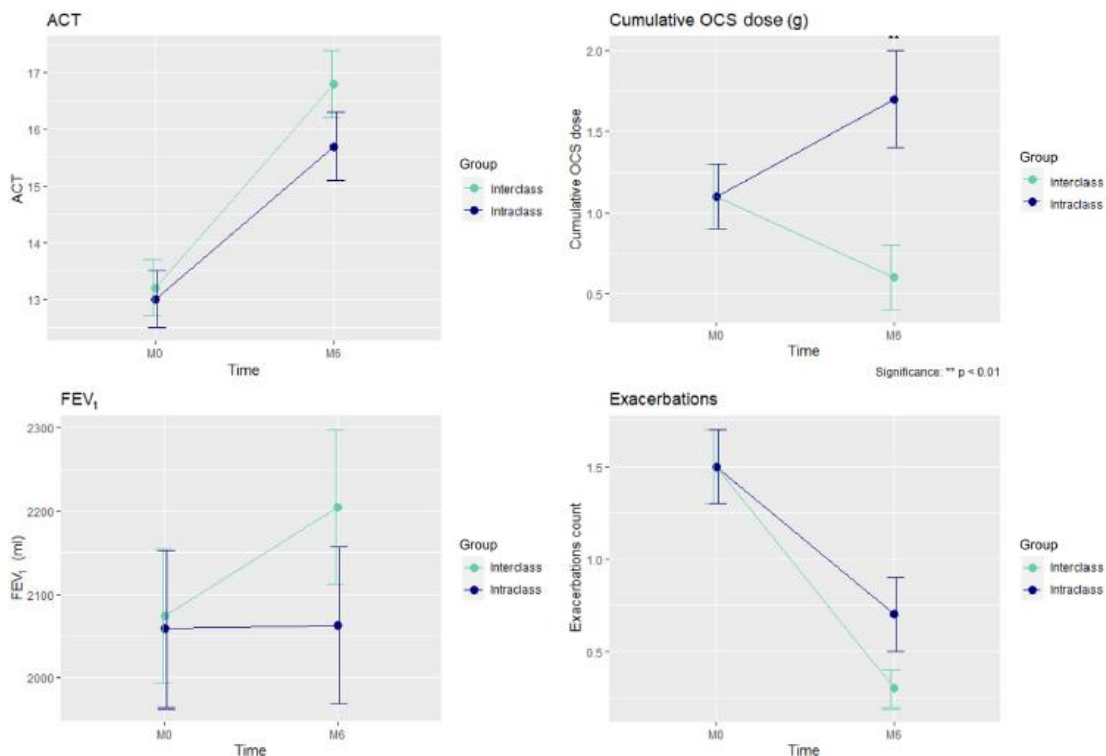
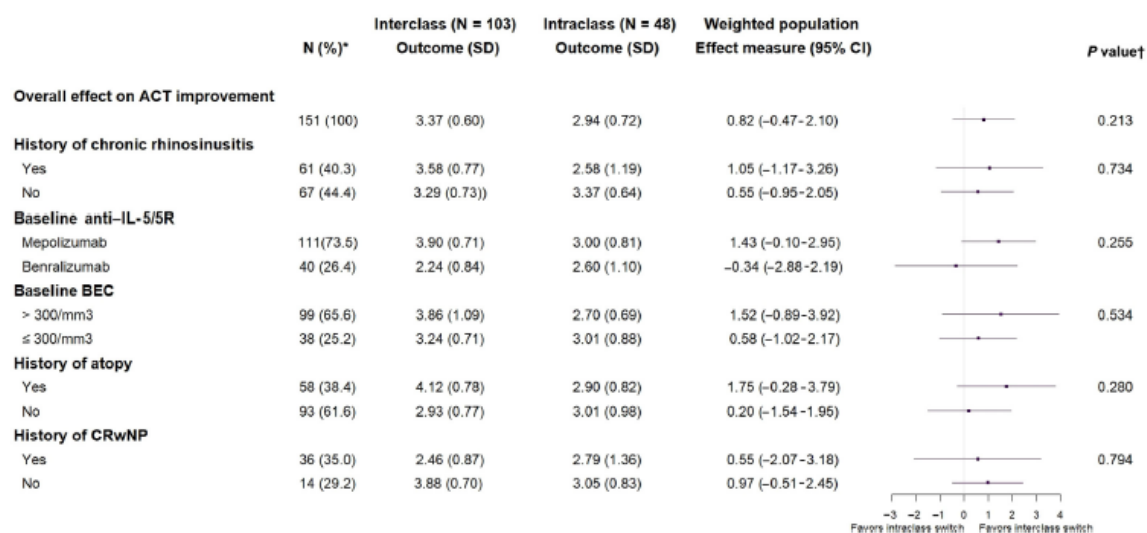


FIG 3. Main outcome changes in the weighted population at 6 months.

One primary strength of this study is its use of a target trial emulation approach for this observational analysis,<sup>18</sup> which substantially aided in mitigating biases, notably immortal time bias. Immortal time bias can manifest as either selection or information bias, occurring when the initiation of follow-up, fulfillment of eligibility criteria, and assignment of

participants to treatment groups do not synchronize temporally. A notable strength of the target trial emulation approach is its precise definition of the 3 key moments (commencement of follow-up, evaluation of eligibility criteria, and allocation to treatment), thus providing the opportunity to effectively mitigate immortal time bias in the analysis.<sup>20,30</sup> Second, previous real-life studies of switching strategies were limited by small sample sizes (10-60 patients).<sup>10,11,13,14,31</sup>

Third, we used a propensity score analysis to adjust for confounders at baseline, which is an adequate method to assess causal effects of interventions with observational data.<sup>32</sup> Fourth, we performed several sensitivity analyses that attested to the robustness of our results. Fifth, RAMSES is a nationwide cohort (52 centers) including patients from private pulmonologists and those from secondary and tertiary university care centers.<sup>17</sup> This varied inclusion lends strong external validity. Finally, comparative effectiveness analyses combined data from pivotal trials that usually excluded patients with comorbidities, who were present in our cohort.<sup>33</sup>



**FIG 4.** Subgroup analyses of the primary outcome according to chronic rhinosinusitis history, the anti-IL-5/5R drug received before the switch and baseline BEC. Atopy was defined as positive prick test result and/or specific IgE for 1 or more common aeroallergen. <sup>\*</sup>Number of participants in the baseline population overall and in each subgroup before imputation of missing data. <sup>†</sup>For subgroups, P values for interaction are shown.

This study has several limitations, mainly related to its observational design: the lack of masking may introduce measurement and performance biases, with remaining potential unmeasured confounders. Second, the statistical power of the study was constrained. Indeed, to estimate the causal effect of the switches, eligibility criteria were restricted to include only those patients who could theoretically receive both treatment strategies, as would be done in a randomized trial. As an example, we excluded patients with 2 previous lines with anti-IL-5/5R drug in our analysis. Third, the rate of missing data was rather high, although we used multiple imputation to handle it, and results were consistent when imputing data with the median. Finally, treatment sequences may have been affected by the availability of specific treatments, which could explain why most patients initially received mepolizumab (available in 2018 in France) rather than benralizumab before switching treatments. However, given the close introduction dates of benralizumab and dupilumab to the French market (2019-2020), the concept of a novelty effect seems less convincing. In our study, only 1 participant switched treatments before January 2020. Moreover, following French asthma guidelines, decisions regarding biologic therapies are typically made during asthma multidisciplinary

meetings attended by pulmonologists, allergists, and ear-nose-throat specialists. This proactive approach likely minimized treatment switches motivated by an anticipation of newer, potentially superior medications.

The ACT score significantly improved at 6 months in both groups, with no significant difference between the 2 switching strategies. These data agree with previous observational studies in which both switching strategies increased the ACT score within a similar range of 2 to 3 points.<sup>10,11,13</sup> We acknowledge that our study may have been underpowered, in part because of a high rate of missing data for this outcome than anticipated.

Our results on the reduction of OCS doses, a major goal when initiating a biologic,<sup>34</sup> also agree with those of previously published studies. A consistent finding across these studies was the reduction in the OCS dose after switching biologics,<sup>11,35-37</sup> regardless of the strategy used. In a study from Japan, the OCS intake was reduced by 33% from baseline when patients were switched to dupilumab from an anti-IL-5/5R mAb,<sup>38</sup> and 2 real-life studies reported from 45% to 50% OCS tapering when an intraclass switch was used.<sup>11,15</sup> Of note, in the present study, OCS use was increased in the intraclass group (though not significantly), although the exacerbation rate decreased. Some courses of OCS may be associated with CRwNP symptoms rather than asthma exacerbation. In fact, 57% of cases reported partial response to anti-IL-5/5R treatment because of the persistence of nasal symptoms.<sup>39</sup> However, we were unable to investigate the impact of persistent CRwNP symptoms on the investigator's decision to switch the biologic and the effect of CRwNP on OCS consumption.

In the present study, transitioning patients from anti-IL-5/5R to anti-IL-4R treatment resulted in a more substantial reduction in exacerbations over 6 months as compared with intraclass switching, although the difference was not statistically significant. Moreover, the interclass group experienced an 80% reduction in exacerbation rate over 6 months, whereas the intraclass group experienced a 53.3% reduction (Table E4). This finding was supported by an OR favoring a switch to dupilumab, with a 50% reduction in exacerbation rate (OR, 3.08; 95% CI, 1.18 to 7.97; P =.068). Randomized controlled trials demonstrated a similar reduction in exacerbation rate for dupilumab (48%), benralizumab (28%-50%), and mepolizumab (47%) versus placebo.<sup>1-3,40</sup> Nonetheless, according to a recent Bayesian network meta-analysis, dupilumab could significantly outperform benralizumab in reducing exacerbations.<sup>41</sup> In addition, a target trial emulation analysis performed by the same team suggested that dupilumab was better than mepolizumab in reducing exacerbations in first line treatment.<sup>42</sup>

We also found improvement in FEV1, although not significant, when switching to an anti-IL-4R mAb. This finding agrees with indirect comparisons in randomized controlled trials and observational studies, which again suggests greater improvement in lung function with dupilumab.<sup>1,41,42</sup> From a pathophysiological perspective, focusing on IL-4 and IL-13 pathways may account for the potential superiority of dupilumab versus anti-IL-5/5R drugs, given a broader anti-inflammatory impact and influence on hyperresponsiveness and remodeling.<sup>43,44</sup> Whether some patients with insufficient response to anti-IL-5/5R drugs have a specific inflammatory pattern, more sensitive to IL-4 and IL-13 pathway blockade, or insufficiently blocked by anti-IL-5<sup>45</sup> remains to be investigated.

## Conclusion

For patients with severe eosinophilic asthma and insufficient response to an anti-IL-5/5R mAb, switching to dupilumab or another anti-IL-5/5R was associated with similar improvement in the ACT score at 6 months. However, switching to dupilumab might be more effective in reducing the use of OCS and to a lesser extent, minimizing exacerbations and improving FEV1. Larger studies are warranted to confirm these results.

### DISCLOSURE STATEMENT

The RAMSES cohort is funded by the French Pneumology Society (SPLF, Société de Pneumologie de Langue Française), AstraZeneca, GlaxoSmithKline, Sanofi as well as Boston Scientific and Novartis. The funders were not involved in the study initiative, statistical analysis plan, interpretation of results, and decision to publish the current study. The Délégation à la Recherche Clinique et à l'Innovation de l'Assistance Publique-Hôpitaux de Paris is the sponsor of the RAMSES cohort. S.V. was awarded a research grant "An ée Recherche" by the Regional Health Agency (Agence Régionale de Santé, Ile-de-France).

Disclosure of potential conflict of interest: C. Taillé received fees from Sanofi, AstraZeneca, GlaxoSmithKline, and Novartis for advisory board education and has been an investigator for trials sponsored by Sanofi, AstraZeneca, GlaxoSmithKline, and Novartis, outside of this work. C. Chenivresse received grants from AstraZeneca, GlaxoSmithKline, Novartis, and Santelys, personal fees from ALK-Abello, AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, and Sanofi-Regeneron, and congress support from AstraZeneca, Boehringer-Ingelheim, Chiesi, Novartis, and Sanofi-Regeneron. G. Devouassoux received grants for clinical research from GlaxoSmithKline and Sanofi, consulting fees from Sanofi, AstraZeneca, GlaxoSmithKline, Chiesi, Menarini, and ALK, payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from Sanofi, AstraZeneca, GlaxoSmithKline, Chiesi, Menarini, and ALK, and for expert testimony and attending meetings and/ for travel from Sanofi, AstraZeneca, and GlaxoSmithKline. P. Bonniaud received research grants from AstraZeneca, payment or honoraria for symposium from Sanofi and AstraZeneca, support for attending medical and research meetings from AstraZeneca, Novartis, Sanofi, Boehringer, and Stallergene, and personal fees for advisory board from AstraZeneca, Novartis, Sanofi, GlaxoSmithKline, and Boehringer. A. Beurnier received payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca and Sanofi. A. Bourdin received grants or contracts from AstraZeneca, Boeringher, and GlaxoSmithKline, consulting fees from AstraZeneca, Sanofi, GlaxoSmithKline, Chiesi, Celtrion, Boeringher, and Novartis, payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca, Sanofi-Regeneron, GlaxoSmithKline, Boeringher, and Novartis, support for attending meetings and/or travel from AstraZeneca and Sanofi, and participation on a Data Safety Monitoring Board or Advisory Board from ABscience. A. Boudjemaa received consulting fees from AstraZeneca, payment or honoraria for lectures, presentations, speaker bureaus, manuscript writing, or educational events from AstraZeneca, Sanofi Genzyme, GlaxoSmithKline, support for attending meetings and/or travel from AstraZeneca, Sanofi Genzyme, and GlaxoSmithKline, and participation on a Data Safety Monitoring Board or Advisory Board from Astra Zeneca, Sanofi Genzyme, GlaxoSmithKline. The rest of the authors declare that they have no relevant conflicts of interest.

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We thank Karima Bourayou, Eve Klising, Nessima Yelles, Sarra Pochon, Amal Gouider, Hadj Kaci Medina, Sellali Yasmine, Dahmani Djouher, Diakhou Ndao, and Yannick Vacher for project management, regulatory, financial, data monitoring, and data management tasks; all clinical research associates from RAMSES centers; and patients participating in the RAMSES cohort. We thank Laura Smales for English correction.

We thank the members of the RAMSES Study Group: Antoine Achkar, Engi Ahmed, Didier Alain, Flora Allibe, Claire Andrejak, Corinne Appere De Vecchi, Cindy Barnig, Camille Begne, Laure Belmont, Guillaume Beltramo, Xavier Blanc, Amandine Briault, Emmanuelle Cadet, Emmanuela Caradec, Emilie Catherinot, Beatrice Cavestri, Alexandre Chabrol, Pascal Chanez, Simon Chauveau, Francis Couturaud, Edouard Cuvillon, Gaëtan Deslee, Toufik Didi, Stéphanie Dirou, Benoît Douvry, Mélanie Drucbert, Clairelyne Dupin, Sandra Dury, Xavier Elharrar, Helen Fouquet, Nathalie Freymond, Stéphanie Fry, Maud Gaillot-Drevon, Anne Sophie Gamez, Gilles Garcia, Wanda Gaspard, Alice Gicquello, Claire Givel, Benoît Godbert, Jésus Gonzalez, Marion Gouitaa, François Goupil, Céline Goyard, Nicolas Guibert, Laurent Guilleminault, Stéphanie Habib-Maillard, Samra Hadjadj, Armine Izadifar, Romain Jean, Marie Jouvenot, Stéphane Jouveshomme, Nicolas Just, Aurélien Justet, Sophia Keddache, Naji Khayath, Bertrand Lemaire, Christophe Leroyer, Xing Li, Antoine Magnan, Bernard Maitre, Gilles Mangiapan, Victor Margelidon, Pascale Martin, Stéphanie Martinez, Laura Mattei, Cyril Maurer, Magalie Mercy, Karine Michaux, Antoine Moui, Gisèle Mourin, Elisa Noel-Savina, Cécile Olivier, Jean-Philippe Oster, Nicolas Paleiron, Audrey Paris, Hervé Pegliasco, Jeanne-Marie Perotin Collard, Julie Perrin, Gaël Picart, Christophe Pison, Elisabeth Popin-Meyer, Laurent Portel, Hassina Rami, Stéphane Raymond, Mireille Rocca Serra, Cécile Rochefort-Morel, Stéphanie Romanet, Nadine Rossignoli, Pauline Roux, Maud Russier, Christel Saint-Raymond, Sergio Salmeron, Helene Salvator, Caroline Sattler, Lucile Sese, Thibaud Soumagne, Colas Tcherakian, Angélica Tiotiu, Céline Tummino, Judith Valcke-Brossollet, Guillaume Vignal, Mathilde Volpato, and Lidwine Wemeau.



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