







Dupilumab Reduces Asthma Disease Burden and Recurrent SCS Use in Patients with CRSwNP and Coexisting Asthma

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Purpose: Dupilumab significantly reduced the requirement for systemic corticosteroids (SCS) in patients with severe chronic rhinosinusitis with nasal polyps (CRSwNP). Patients with CRSwNP and coexisting asthma typically have a higher disease burden and have more difficulty in managing disease. Here, we report an analysis of asthma outcomes and SCS use in patients with CRSwNP and coexisting asthma.

Patients and Methods: This was a post hoc analysis of the randomized, placebo-controlled SINUS-24 and SINUS-52 studies (NCT02912468/NCT02898454) in patients with severe CRSwNP and coexisting asthma (patient self-reported) from the pooled intention-to-treat population randomized to dupilumab 300 mg every 2 weeks or placebo. On-treatment SCS use was estimated using Kaplan–Meier analysis. Forced expiratory volume in 1 s (FEV₁), percent predicted FEV₁, and the 6-item Asthma Control Questionnaire (ACQ-6) were assessed at baseline and Week 24 (pooled SINUS-24/52) in patients with/without history of asthma exacerbation or prior SCS use.

Results: Of 337 patients with coexisting asthma, 88 (26%) required on-treatment SCS use. The requirement for on-treatment SCS use for any reason was significantly lower with dupilumab (20/167 patients; 12%) vs placebo (68/170; 40%); hazard ratio (95% confidence interval) 0.248 (0.150–0.409); $p < 0.0001$. The most frequent reasons for SCS use were nasal polyps (dupilumab 3% and placebo 27%) and asthma (2% and 9%, respectively). FEV₁, percent predicted FEV₁, and ACQ-6 were all significantly improved at Week 24 with dupilumab vs placebo irrespective of history of asthma exacerbation or prior SCS use (all $p < 0.01$).

Conclusion: Dupilumab significantly reduced the requirement for SCS and improved asthma outcomes irrespective of history of asthma exacerbation or prior SCS use vs placebo in patients with CRSwNP and coexisting asthma, demonstrating concomitant reduction of SCS use and asthma disease burden in these patients.

Plain Language Summary: Chronic rhinosinusitis with nasal polyps (CRSwNP) and asthma are type 2 inflammatory conditions that often coexist. Patients with both CRSwNP and asthma generally have worse symptoms that are more difficult to treat. Their standard treatment is topical (inhaled/intranasal) corticosteroids, but where this is ineffective, systemic corticosteroids, also called SCS, are used. SCS are effective at reducing nasal polyp size and improving symptoms, but this effect often does not last, and many patients experience side effects when SCS are used for a long time. Dupilumab, a drug that targets type 2 inflammation, is approved for treating both uncontrolled CRSwNP and moderate-to-severe asthma. Here, we investigate whether dupilumab changes how often patients with CRSwNP and asthma need to use SCS and its effect on their asthma. We found that dupilumab-treated patients were 75% less likely to need SCS than patients treated with placebo and also had significantly greater improvements in measures of their asthma severity, irrespective of their history of previous asthma attacks or previous SCS use. These results show that, in patients with CRSwNP and

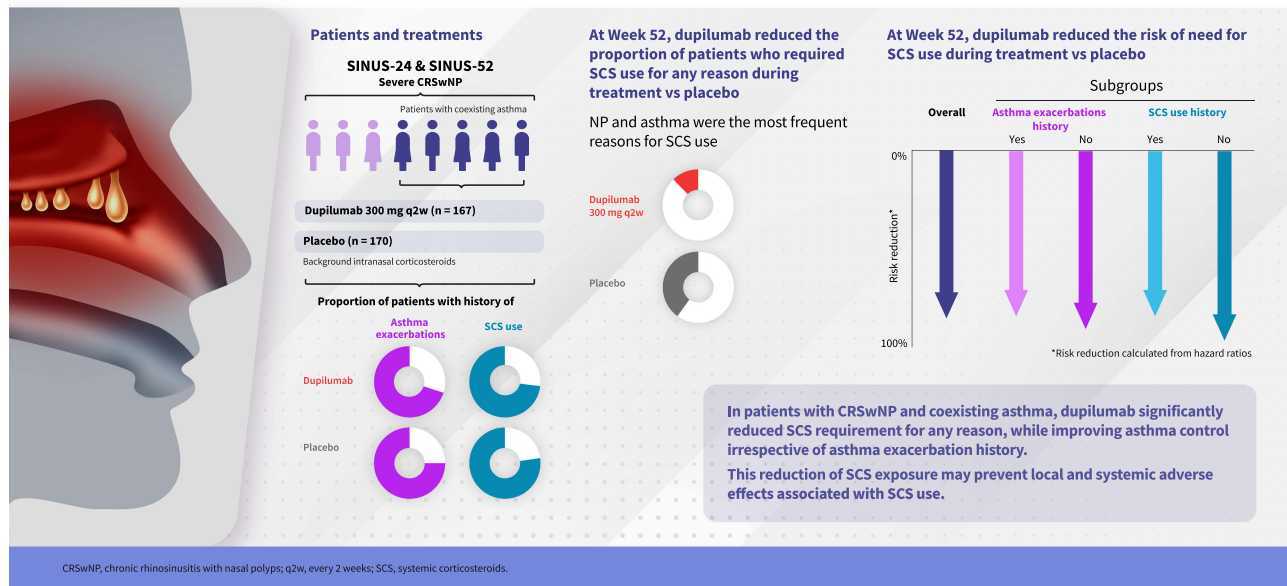
asthma, dupilumab can improve asthma symptoms and reduce the need for SCS use. Using fewer SCS may help patients avoid the side effects associated with SCS use.

Keywords: asthma control, asthma exacerbation, chronic rhinosinusitis with nasal polyps, systemic corticosteroids, LIBERTY SINUS-24, LIBERTY SINUS-52

Graphical Abstract

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DUPILUMAB | 



Introduction

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a predominantly type 2 inflammatory disease that shares inflammatory pathophysiology with asthma, with up to 60% of patients with CRSwNP having coexisting asthma.¹ These patients typically have more severe CRSwNP and asthma that are more difficult to treat, resulting in poorer upper and lower airway outcomes.² Patients with poor symptom control despite use of inhaled nasal corticosteroids are often prescribed systemic corticosteroids (SCS) to address systemic inflammation. Although effective at reducing the size of nasal polyps (NP) and improving symptoms, response is often temporary and long-term use of SCS is associated with adverse local or systemic effects.³ Real-world evidence also suggests that the use of SCS as a rescue therapy may be necessary during treatment with biologics in some patients with CRSwNP.⁴ Dupilumab is a fully human monoclonal antibody that inhibits interleukin (IL)-4 receptor alpha, the shared receptor for IL-4 and IL-13, which are key cytokines driving type 2-mediated inflammation.^{5,6} In the Phase 3 SINUS-24 and SINUS-52 studies in patients with severe CRSwNP (NCT02912468 and NCT02898454), dupilumab significantly reduced the requirement for SCS during the treatment period by 73.9% and the mean number of SCS courses by 75.3% vs placebo, and was generally well tolerated.⁷ Here, we report the findings of a post hoc analysis of SCS use and asthma outcomes in SINUS-24 and SINUS-52 patients with coexisting asthma.

Materials and Methods

The SINUS-24 and SINUS-52 studies have been previously described.⁸ Briefly, eligible patients were ≥ 18 years of age with bilateral NP and symptoms of CRSwNP despite intranasal corticosteroid therapy and had received SCS in the previous 2 years or previous sinonasal surgery. Patients were required to have a bilateral endoscopic nasal polyp score of ≥ 5 (≥ 2 for each nostril) and at least two of moderate-to-severe nasal congestion or obstruction (patient-assessed) and either loss of smell or nasal discharge (anterior or posterior). Patients with coexisting asthma had to be stable in the 6 weeks prior to study entry using their regular asthma treatment. Patients with pre-bronchodilator forced expiratory volume in 1 s (FEV_1) $\leq 50\%$ of predicted normal or those who had participated in prior dupilumab clinical trials were excluded. In SINUS-24, patients were recruited at 67 hospitals or clinical centers in 13 countries. In SINUS-52, patients were recruited at 117 hospitals or clinical centers in 14 countries. Data were collected by investigators at each study site.

In this post hoc analysis, the requirements for SCS use—including the number of courses, dose(s), course duration(s), and time to first use—during the treatment period to Week 52 were assessed. Asthma disease burden was assessed using least squares mean change from baseline to Week 24 for dupilumab vs placebo in the 6-item Asthma Control Questionnaire (ACQ-6, range 0–6), pre-bronchodilator forced expiratory volume in 1 s (FEV_1), and percent predicted FEV_1 . Analyses were conducted on the intention-to-treat population of patients with coexisting asthma, and on subgroups of these patients with and without a history of asthma exacerbation and with and without SCS use within the last 2 years prior to enrollment. Data from SINUS-24 and SINUS-52 were pooled to Week 24 and evaluated to Week 52 in SINUS-52 only.

Results

Overall, at baseline 127/170 (74.7%) and 116/167 (69.5%) patients had a history of asthma exacerbation in the placebo and dupilumab groups, respectively (Table 1 and [Supplementary Figure 1](#)), and 130/170 (76.5%) and 122/167 (73.1%)

Table 1 Baseline Demographics and SCS Use During the Treatment Period

	Placebo (n = 170)	Dupilumab 300 mg q2w (n = 167)
History of asthma exacerbation, n (%) ^a	127 (74.7)	116 (69.5)
SCS use in previous 2 years, n (%)	130 (76.5)	122 (73.1)
Blood eosinophils, 10 ⁹ /L, mean (SD)	0.51 (0.38)	0.54 (0.43)
Baseline FEV_1 , L, mean (SD)		
With history of asthma exacerbation ^a	2.57 (0.85)	2.61 (1.07)
Without history of asthma exacerbation ^a	2.77 (0.76)	2.64 (0.75)
With prior SCS use	2.64 (0.85)	2.70 (1.01)
Without prior SCS use	2.54 (0.77)	2.41 (0.88)
Baseline percent predicted FEV_1 , %, mean (SD)		
With history of asthma exacerbation ^a	83.60 (18.60)	84.67 (22.07)
Without history of asthma exacerbation ^a	87.76 (15.79)	80.99 (18.13)
With prior SCS use	84.25 (16.35)	84.96 (21.89)
Without prior SCS use	85.86 (22.69)	79.69 (17.84)

(Continued)

Table 1 (Continued).

	Placebo (n = 170)	Dupilumab 300 mg q2w (n = 167)
Baseline ACQ-6 score (0–6), mean (SD)		
With history of asthma exacerbation ^a	1.69 (1.14)	1.55 (1.10)
Without history of asthma exacerbation ^a	1.58 (0.93)	1.36 (0.92)
With prior SCS use	1.66 (1.05)	1.48 (1.07)
Without prior SCS use	1.65 (1.22)	1.53 (1.01)
SCS use during the treatment period, n (%)	68 (40.0)	20 (12.0)
Reason for SCS use, n (%) ^b		
NP	45 (66.2)	5 (25.0)
Asthma	16 (23.5)	4 (20.0)
Other respiratory disease	9 (13.2)	4 (20.0)
Other ear, nose, or throat disease	8 (11.8)	2 (10.0)
Other reason	6 (8.8)	11 (55.0)
Number of SCS courses, n (%) ^b		
1	41 (60.3)	11 (55.0)
2	11 (16.2)	6 (30.0)
3	7 (10.3)	2 (10.0)
≥4	9 (13.2)	1 (5.0)
Total SCS duration, days, median (range)	12.0 (1.0–74.0)	6.5 (1.0–263.0)
Prescribed total SCS dose, mg ^c		
Mean (SD)	505.6 (629.4)	575.3 (1134.8)
Median (range)	367.5 (10.0–4700.0)	181.7 (26.7–4871.5)

Notes: ^aAsthma exacerbation was defined as an exacerbation requiring SCS or hospitalization (>24 hours) for treatment of asthma and was determined using medical records. ^bPercentages calculated using the number of patients with SCS use during the treatment period as the denominator (placebo n = 68 and dupilumab n = 20). ^cPrednisone-equivalent dosage.

Abbreviations: ACQ-6, 6-item Asthma Control Questionnaire; FEV₁, forced expiratory volume in 1 s; NP, nasal polyps; q2w, every 2 weeks; SCS, systemic corticosteroids; SD, standard deviation.

had prior SCS use within the last 2 years (Table 1). Most of the treatment subgroups showed patients had inadequately controlled asthma at baseline (Table 1).

During the treatment period, a total of 88 patients received SCS, with prednisone the most commonly used SCS (n = 42), and NP and asthma the most frequent reasons for SCS use (Table 1). Dupilumab-treated patients had less exposure to SCS than those in the placebo group, demonstrated by reduced on-treatment SCS courses, total course duration, and median cumulative prednisone-equivalent dose (Table 1). The requirement for on-treatment SCS was significantly lower with dupilumab compared with placebo in the overall patient population (Figure 1A) and in subgroups of patients with or without a baseline history of asthma exacerbation (Figure 1B) or prior SCS use (Figure 1C).

Significant improvements from baseline were observed with dupilumab vs placebo at Week 24 in ACQ-6, FEV₁, and percent predicted FEV₁, irrespective of prior history of asthma exacerbation or prior SCS use (Supplementary Figure 2; dupilumab vs placebo $p \leq 0.0016$ for all outcomes). No significant differences were observed between patients with or

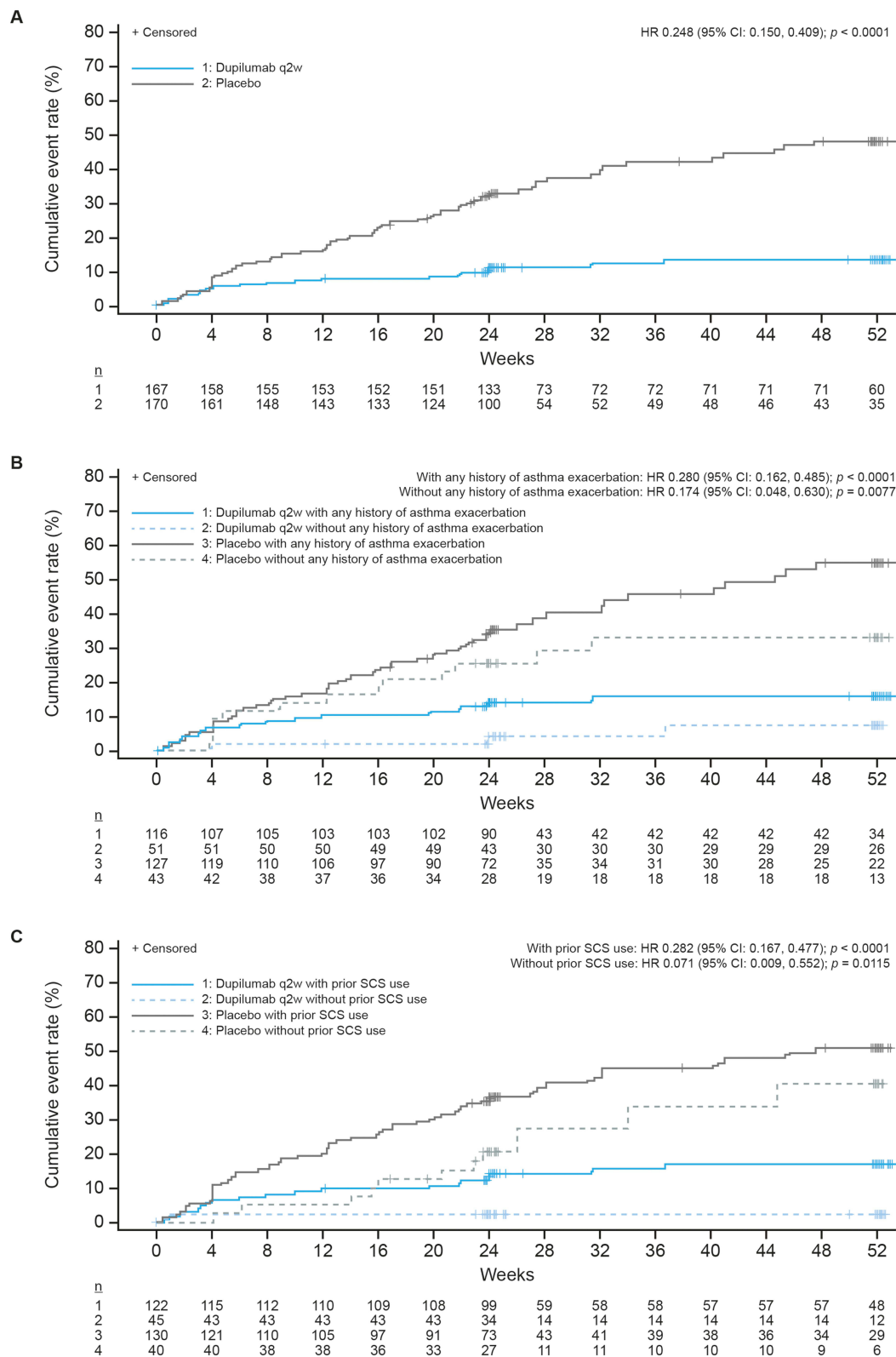


Figure 1 Kaplan–Meier plot of time to first use of SCS during the treatment period in patients with CRSwNP and coexisting asthma **(A)** overall and **(B)** by history of asthma exacerbation^a or **(C)** prior SCS use.

Notes: ^aAsthma exacerbation was defined as an exacerbation requiring SCS or hospitalization (>24 hours) for treatment of asthma and was determined using medical records. All *p*-values are nominal.

Abbreviations: CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; HR, hazard ratio; q2w, every 2 weeks; SCS, systemic corticosteroids.

without a history of asthma exacerbation or between patients with or without prior SCS use for any of the three outcomes assessed (all interactions $p > 0.45$).

Discussion

In this post hoc analysis of patients with severe CRSwNP and coexisting asthma from the SINUS-24 and SINUS-52 studies, dupilumab reduced the requirement for SCS, used mostly for NP and/or asthma exacerbation. Furthermore, the duration of SCS use, recurrent SCS use, and median prescribed SCS dose were all significantly reduced with dupilumab compared with placebo. This reduction in SCS exposure may prevent local and systemic adverse effects in patients, as seen with steroid-sparing strategies in severe asthma.⁹ Asthma control, as measured by ACQ-6, was improved with dupilumab irrespective of asthma exacerbation history and prior SCS use, demonstrating concomitant reduction of asthma disease burden and SCS use.

The common coexistence of asthma and CRSwNP has given rise to the concept of united airway disease, which is thought to be caused by type 2 inflammatory pathophysiology manifesting as a disease in both the upper and lower airways.^{10,11} Patients with coexisting asthma typically have more severe CRSwNP that is recalcitrant to standard treatments.¹² However, the results presented here suggest that dupilumab represents a viable therapeutic alternative for these difficult-to-treat patients with NP. Another recent analysis of the SINUS population demonstrated dupilumab efficacy in patients with CRSwNP and coexisting asthma irrespective of the severity of their asthma at baseline,¹³ while the TRAVERSE study demonstrated dupilumab efficacy in patients with Global Initiative for Asthma (GINA)-defined type 2 asthma and CRSwNP.¹⁴ The efficacy of dupilumab in CRSwNP and asthma may be explained by its mechanism of action in targeting IL-4 and IL-13, which are key drivers of type 2 inflammation in both diseases,^{5,6} with more than 95% of the overall SINUS population having type 2 inflammatory disease on the basis of a range of biomarkers and clinical measures.¹⁵

Limitations of this analysis include its post hoc nature and the categorization of patients with asthma on the basis of self-reporting by the study participants. To address these, prospective randomized studies involving patients with severe CRSwNP and a confirmed diagnosis of asthma based on clinical guidelines would be informative and provide additional evidence in a more stringently diagnosed patient population. A further limitation relates to the time period of the original SINUS studies (conducted between 2016 and 2017), as guidelines on the use of SCS to control severe asthma have evolved since then, which may limit the generalizability of the results to patients with CRSwNP and coexisting asthma currently.

Conclusion

This post hoc analysis demonstrates that dupilumab treatment provides asthma control while reducing SCS usage and treatment burden in patients with the type 2 disease of CRSwNP and coexisting asthma. This also confirms that this treatment improves patient quality of life while decreasing reliance on SCS use, which can be associated with local and systemic adverse effects.

Abbreviations

ACQ-6, 6-item Asthma Control Questionnaire; CI, confidence interval; CRSwNP, chronic rhinosinusitis with nasal polyps; FEV₁, forced expiratory volume in 1 s; HR, hazard ratio; IL, interleukin; NP, nasal polyps; q2w, every 2 weeks; SCS, systemic corticosteroids.

Data Sharing Statement

Qualified researchers may request access to patient-level data and related study documents including clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient-level data will be anonymized, and study documents will be redacted to protect the privacy of trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: <https://www.vivli.org/>.

Ethics Approval and Informed Consent

The SINUS-24 and SINUS-52 studies were conducted according to the Declaration of Helsinki principles and were approved by the local institutional review board or ethics committee at each study site ([Supplementary Table S1](#)). All patients provided written informed consent.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

Mark Gurnell reports steering committee membership and speakers' bureau fees for AstraZeneca, and speakers' bureau fees for Novartis. Amr Radwan, Scott Nash, and Yamo Deniz are employees of Regeneron Pharmaceuticals Inc. and may hold stock and/or stock options in the company. Claus Bachert reports grants from Sanofi and was the principal investigator for studies for Sanofi, GlaxoSmithKline, and Novartis, during the conduct of the study. Njira Lugogo is an advisory board member and has received consultancy fees from Novartis, has received research grants from Avillion and Gossamer Bio, and is an advisory board member and has received consultancy fees and research grants from AstraZeneca, Genentech, GlaxoSmithKline, Regeneron Pharmaceuticals Inc., Sanofi, and Teva Pharmaceutical Industries Ltd. Seong H Cho has received grants from and is an advisory board member for Sanofi, and Regeneron, during the conduct of the study; received grants from the National Institute of Health, and received research grants from and is an advisory board member for Insmid, outside the submitted work. Haixin Zhang is a former employee of Regeneron Pharmaceuticals Inc. and may hold stock and/or stock options in the company. Asif H Khan, Juby A Jacob-Nara, and Paul J Rowe are employees of Sanofi and may hold stock and/or stock options in the company.

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