ITA: nouveautés …2013…

Pneumo-allergologie pédiatrique
CHPLT de Verviers

Dr. Bénédicte Derkenne
Dr. Karin Giebels
Dr. Thierry Carvelli

LEVELS OF EVIDENCE

1++	High quality meta-analyses, systematic reviews of randomised controlled trials (RCTs), or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case control or cohort studies High quality case control or cohort studies with a very low risk of confounding c bias and a high probability that the relationship is causal
2+	Well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

GRADES OF RECOMMENDATION

EBM

Note: The grade of recommendation relates to the strength of the evidence on which the recommendation is based. It does not reflect the clinical importance of the recommendation.

A	At least one meta-analysis, systematic review of RCTs, or RCT rated as 1++ and directly applicable to the target population; *or* A body of evidence consisting principally of studies rated as 1+, directly applicable to the target population, and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++, directly applicable to the target population, and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results; *or* Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; *or* Extrapolated evidence from studies rated as 2+

GOOD PRACTICE POINTS

☑	Recommended best practice based on the clinical experience of the guideline development group

Allergen Immunotherapy

1911	1960	1970	1986	1998	2000	2005	2006	2007	2008	2013
SCIT	First RCT SCIT	SLIT	First RCT SLIT	WHO	ARIA	First Meta SLIT	Large RCT SCIT	First Meta SCIT	Large RCT SLIT	EBM

CHEST Original Research

ASTHMA

Metaanalysis of the Efficacy of Sublingual Immunotherapy in the Treatment of Allergic Asthma in Pediatric Patients, 3 to 18 Years of Age*

Martin Penagos, MD, MSc; Giovanni Passalacqua, MD; Enrico Compalati, MD; Carlos E. Baena-Cagnani, MD; Socorro Orozco, MD; Alvaro Pedroza, MD; and Giorgio Walter Canonica, MD

9 /73 études acceptées: 441 patients

Pollinoses: olivier, graminée, mélange pollen G/B…,

Acariens

(CHEST 2008; 133:599–609)

Effet long terme de l'immunothérapie sublinguale chez les enfant souffrants

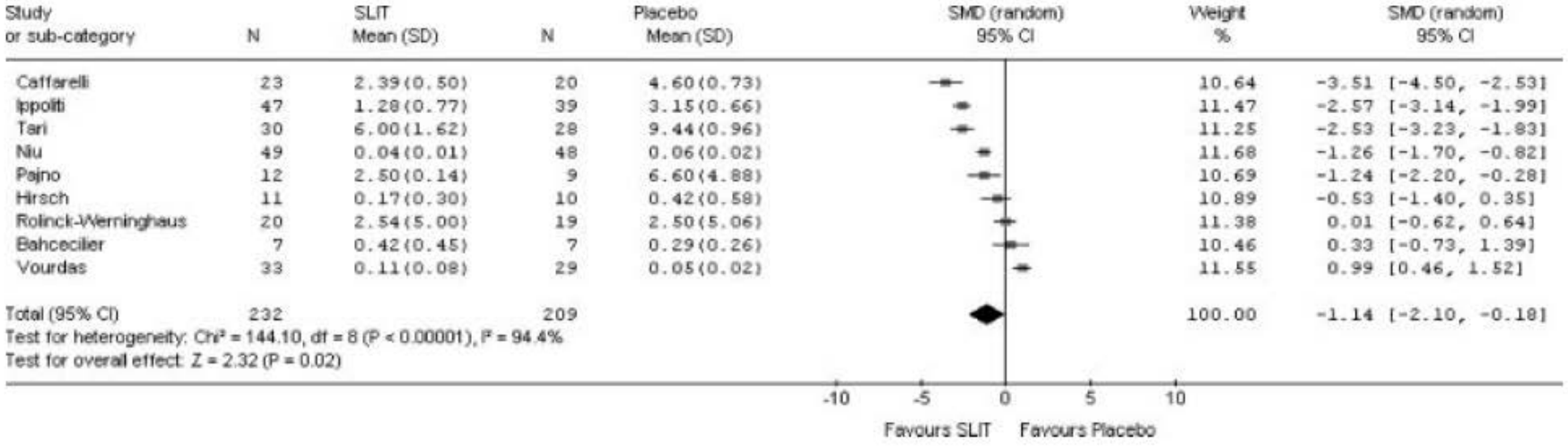

FIGURE 2. Outcome: asthma score.

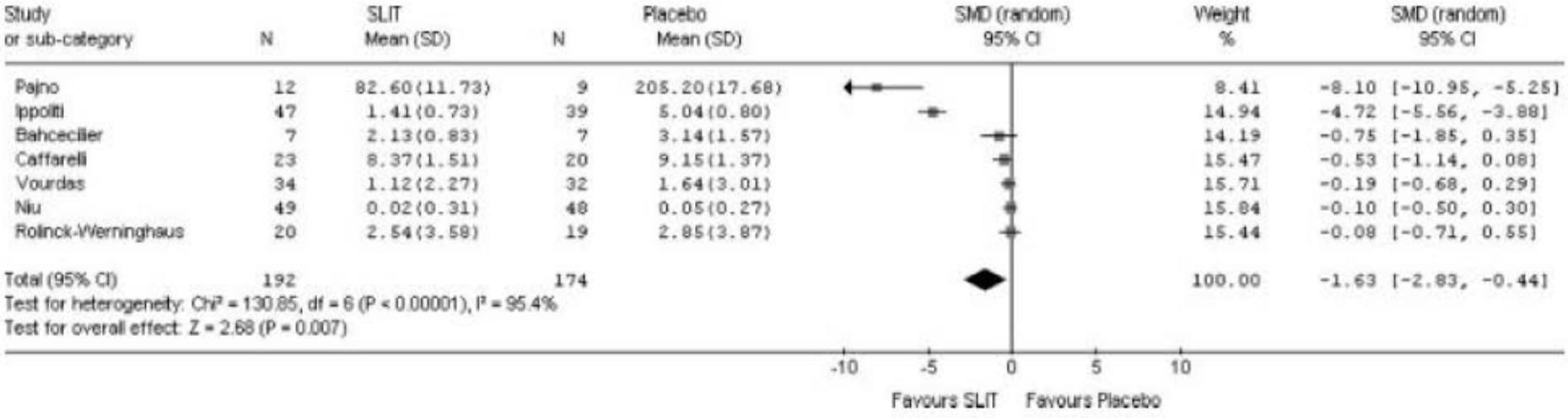

FIGURE 3. Outcome: medication score.

Effet long terme de l'immunothérapie sublinguale chez les enfant souffrants d'asthme d'asthme

Background: Recent studies have documented the efficacy and safety of sublingual immunotherapy (SLIT) in patients with rhinitis, but the value of this treatment in those with asthma is still debated. We evaluated the efficacy of SLIT in the treatment of allergic asthma in children by a metaanalysis of randomized, double-blind, and placebo-controlled (DBPC) clinical trials.

Methods: Electronic databases were searched up to May 31, 2006, for randomized DBPC trials assessing SLIT in pediatric cases of asthma. Effects on primary outcomes (*ie*, symptom scores and concomitant use of rescue medication) were calculated with standardized mean differences (SMDs) using the random-effects model. We performed the metaanalysis using a statistical software package (RevMan, 4.2.8; The Cochrane Collaboration; Oxford, UK), and we followed the recommendations of the Cochrane Collaboration and the Quality of Reporting of Metaanalyses guidelines.

Results: Seventy-three articles were identified and reviewed. Nine studies, all published after 1990, fulfilled the selection criteria. A total of 441 patients had a final assessment and were included in the analysis. Two hundred thirty-two patients received SLIT, and 209 patients received placebo. The results of the present analysis demonstrated a relevant heterogeneity due to widely differing scoring systems. Overall, there was a significant reduction in both symptoms (SMD − 1.14; 95% confidence interval [CI], − 2.10 to − 0.18; p = 0.02) and medication use (SMD, − 1.63; 95% CI, − 2.83 to − 0.44; p = 0.007) following SLIT.

Conclusion: SLIT with standardized extracts reduces both symptom scores and rescue medication use in children with allergic asthma compared with placebo. *(CHEST 2008; 133:599–609)*

les enfant souffrants d'asthme

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Systematic reviews of sublingual immunotherapy (SLIT)

S. Radulovic[1], D. Wilson[2], M. Calderon[3] & S. Durham[3] Allergy 2011; DOI: 10.1111/j.1398-9995.2011.02583.x.

[1]Paediatric Allergy, King's College, London; [2]Selly Oak Hospital, University Hospitals Birmingham NHS Trust, Birmingham, UK; [3]Royal Brompton Hospital, Upper Respiratory Medicine, London, UK

2011

Abstract

Allergic rhinitis is common worldwide, with significant morbidity and impact on quality of life. In patients who don't respond adequately to anti-allergic drugs. Subcutaneous allergen immunotherapy is effective although requires specialist administration. Sublingual immunotherapy may represent an effective and safer alternative. This Cochrane systematic review is an update of one published in 2003. We searched Cochrane ENT Group Trials Register, Central, PubMed, EMBASE, CINAHL, Web of Science, Biosis Previews, Cambridge Scientific Abstarcts, mRCT and additional sources. We included randomised, double-blind, placebo- controlled trials of sublingual immunotherapy in adults and children. Two authors selected studies and assessed them for quality. Data were put into RevMan 5.0 for a statistical analysis. We used standardised mean difference (SMD), with a random effect model to combine data. Sixty studies were included, with 49 suitable for meta-analysis. We found significant reductions in symptoms (SMD −0.49; 95%CI (−0.64 to −0.34, $P < 0.00001$)) and medication requirements (SMD −0.32; 95%CI (−0.43 to −0.21, $P < 0.00001$)) compared with placebo. None of the trials reported severe systemic reactions, anaphylaxis or use of Adrenaline. This updated review reinforces the conclusion of the original 2003 Cochrane Review that sublingual immunotherapy is effective for allergic rhinitis and appears a safe route of administration.

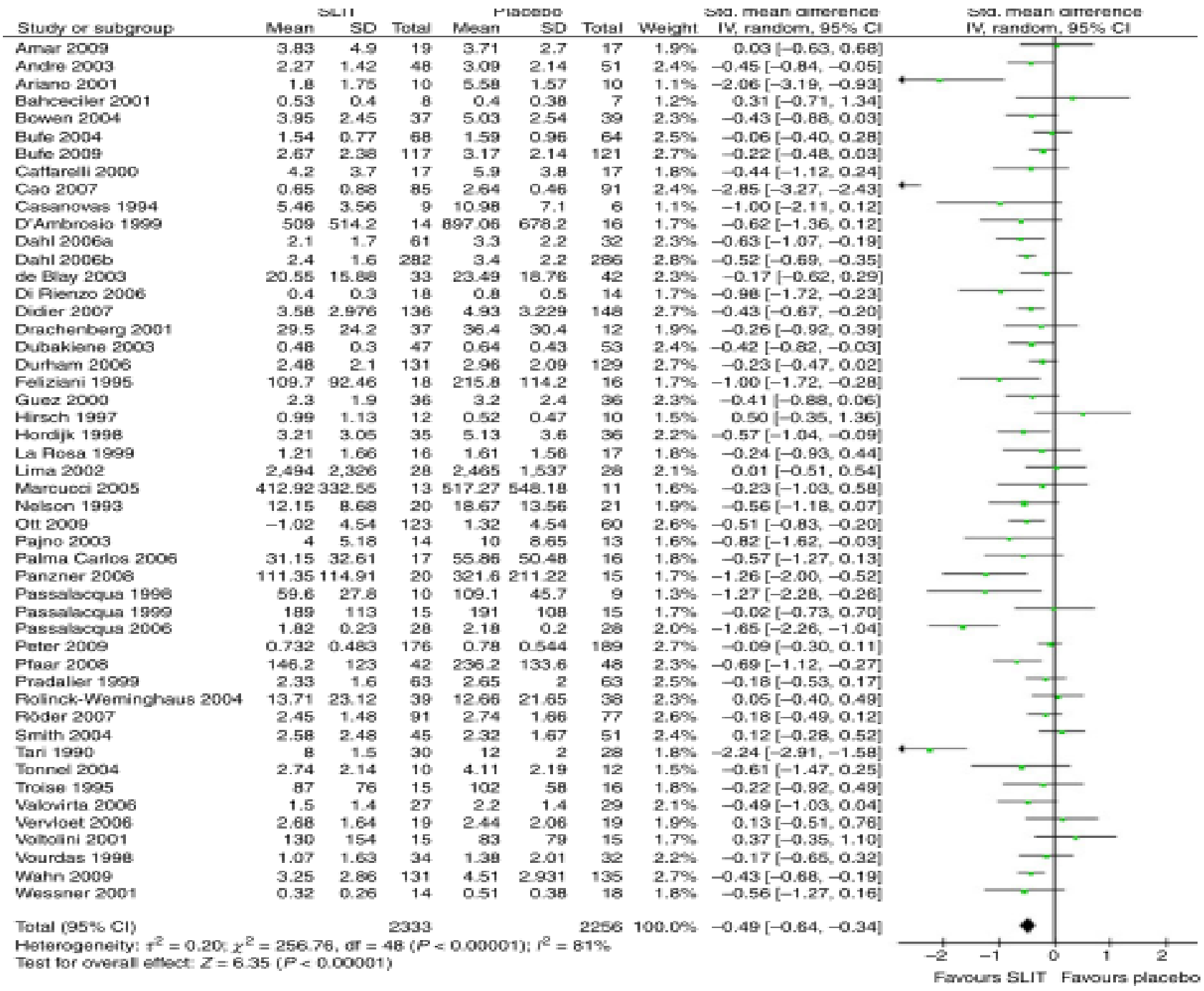

Figure 2 Symptom scores-all.

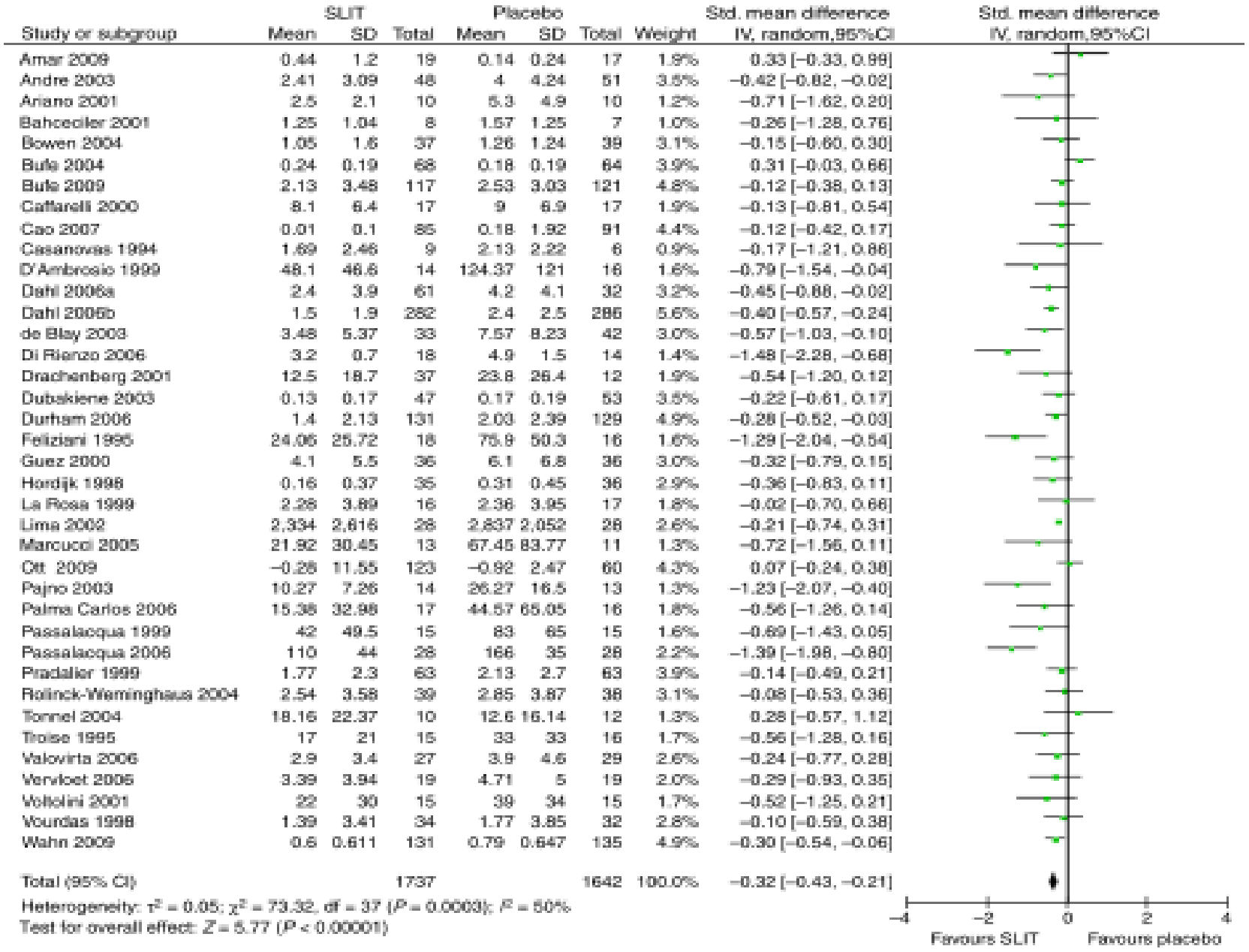

Figure 3 Medication scores-all.

Systematic reviews of sublingual immunotherapy (SLIT)

S. Radulovic[1], D. Wilson[2], M. Calderon[3] & S. Durham[3]

[1]Paediatric Allergy, King's College, London; [2]Selly Oak Hospital, University Hospitals Birmingham NHS Trust, Birmingham, UK; [3]Royal Brompton Hospital, Upper Respiratory Medicine, London, UK

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SIT (Abramson Cochrane review 2003)
Réaction allergique généralisée 1/1250 à 1/2206
Near fatal 5,4 /1 million
Décès 1 à 2 /1 million
FR: Asthme non contrôlé , VEMS < nle

SLIT induced-anaphylaxis - Published case-reports

1. Anaphylaxis to sublingual immunotherapy. *Dunsky EH. et al. Allergy 2006 ; 61 : 1235*

   A poorly described case-report – mixture of 6 allergens (probably not standardized)

2. Anaphylaxis by latex sublingual immunotherapy. *Antico A. et al. Allergy 2006 ; 61 : 1236-37*

   Latex is not commonly used for SLIT + rush protocol

3. Anaphylaxis to multiple pollen allergen sublingual immunotherapy (Staloral) *Eifan AO. et al. Allergy 2007; 62 : 567- 68*

   A severe local adverse reaction not an anaphylactic shock

4. Anaphylactic shock because of sublingual immunotherapy (Staloral) overdose during third year of maintenance dose. *Blazowski I. Allergy 2008; 63:374*

   *After a long period of SLIT cessation the patient restarted with a very high dose **without medical supervision***

5. Anaphylactic reaction after the first dose of sublingual immunotherapy with grass pollen tablet (Grazax). *de Groot H., Bijl A. Allergy 2009: 64: 961–967*

   *Two anaphylactic reactions after **first** dose of grass pollen **tablet,** resulting in a **strict advice to take the first tablet under medical observation**.*

Table 27 - Level of evidence of different interventions in allergic rhinitis

The level of evidence was made according to Shekelle et al [12]
Adapted from [24-28]

ARIA 2008

intervention		Seasonal rhinitis		Perennial rhinitis (mostly applies for studies ≤ 4 weeks)*		Persistent rhinitis[$]
		adult	children	adult	children	
H_1-anti-histamine						
	Oral	A	A	A	A	A
	Intranasal	A	A	A	A	No data
	Intraocular	A	A	B	B	No data
Glucocorticosteroid						
	Intranasal	A	A	A	A	No data
	Oral	A	B	B	B	No data
	IM	A	B	B	B	No data
Cromones						
	Intranasal	A	A	A	B	No data
	Intraocular	A	A	B	B	No data
Naaga (topical)		B	C	C	C	No data
Anti-leukotriene		A	A over 6 yrs			No data
Decongestant						
	Intranasal	C	C	C	C	No data
	Oral	A				No data
	Oral + H_1-antihistamine	A	B	B	B	No data
Anti-cholinergic				A	A	No data
Homeopathy		D	D	D	D	No data
Acupuncture		D	D	D	D	No data
Phytotherapy		B	D	D	D	No data
Other CAM		D	D	D	D	No data
Specific immunotherapy: rhinoconjunctivitis						
	Subcutaneous	A	A	A	A	No data
	Sublingual**	A	A	A	A	No data
	Intranasal**	A				No data
Specific immunotherapy: asthma						
	Subcutaneous	A	A	A	A	
	Sublingual**	A	A	A	A	
Anti-IgE		A	A over 12 yrs	A	A over 12 yrs	No data
Allergen avoidance						
	House dust mites	D	D	D	D	No data
	Other indoor allergens	D	D	D	D	No data
	Total avoidance of occupational agent			A (for asthma)		No data
	Partial avoidance of latex			B		No data

*: Very few studies longer than 4 weeks

Recommendations of AIT for HDM allergy

2010

ARIA

"Conditional recommendation"

SCIT/SLIT adults: moderate quality evidence
SCIT/SLIT children: low quality evidence

Brożek J et al. ARIA Revision 2010. J Allergy Clin Immunol 2010;126:466-76

2011

GINA

"AIT should be considered only after strict environmental avoidance and pharmacological intervention"

GINA global strategy for asthma management and prevention: updated 2012

e only

Intermittent Asthma

Persistent Asthma: Daily Medication

Consult with asthma specialist if step 4 care or higher is required.
Consider consultation at step 3.

Follow up

Step 1

Preferred:

SABA PRN

Step 2

Preferred:

Low-dose ICS

Alternative:

Cromolyn, LTRA, Nedocromil, or Theophylline

Step 3

Preferred:

Low-dose ICS + LABA

OR

Medium-dose ICS

Alternative:

Low-dose ICS + either LTRA, Theophylline, or Zileuton

Step 4

Preferred:

Medium-dose ICS + LABA

Alternative:

Medium-dose ICS + either LTRA, Theophylline, or Zileuton

Step 5

Preferred:

High-dose ICS + LABA

AND

Consider Omalizumab for patients who have allergies

Step 6

Preferred:

High-dose ICS + LABA + oral corticosteroid

AND

Consider Omalizumab for patients who have allergies

Step up if needed

(first, check adherence, environmental control, and comorbid conditions)

Assess control

Step down if possible

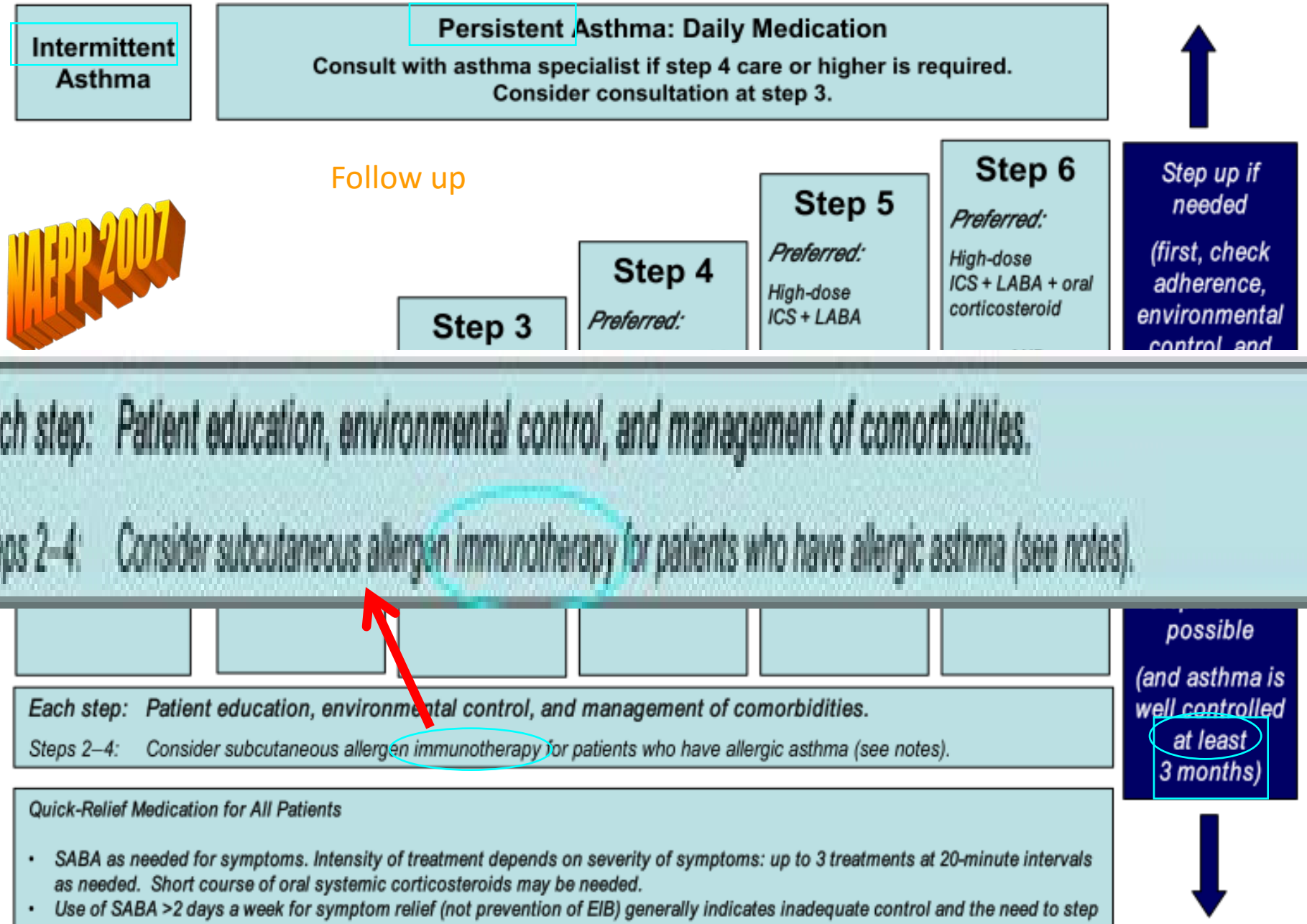
(and asthma is well controlled at least 3 months)

Each step: Patient education, environmental control, and management of comorbidities.

Steps 2–4: Consider subcutaneous allergen immunotherapy for patients who have allergic asthma (see notes).

Quick-Relief Medication for All Patients

- *SABA as needed for symptoms. Intensity of treatment depends on severity of symptoms: up to 3 treatments at 20-minute intervals as needed. Short course of oral systemic corticosteroids may be needed.*
- *Use of SABA >2 days a week for symptom relief (not prevention of EIB) generally indicates inadequate control and the need to step up treatment.*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NAEPP 2007
Step 3
Step 4
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Allergen Immunotherapy for Rhinitis

SCIT

All allergens

8 studies (187 active/ 189 placebo)
SMD (95% CI) = -0.86 (-1.48; -0.23)
p = 0.007
I^2 = 86%

Calderon M et al. Cochrane Database Syst Rev. 2013

Sub-analysis for HDM only

7 studies (173 active/ 175 placebo)
SMD (95% CI) = -1.07 (-1.67; -0.48)
p = 0.0004
I^2 = 83%

SLIT

All allergens

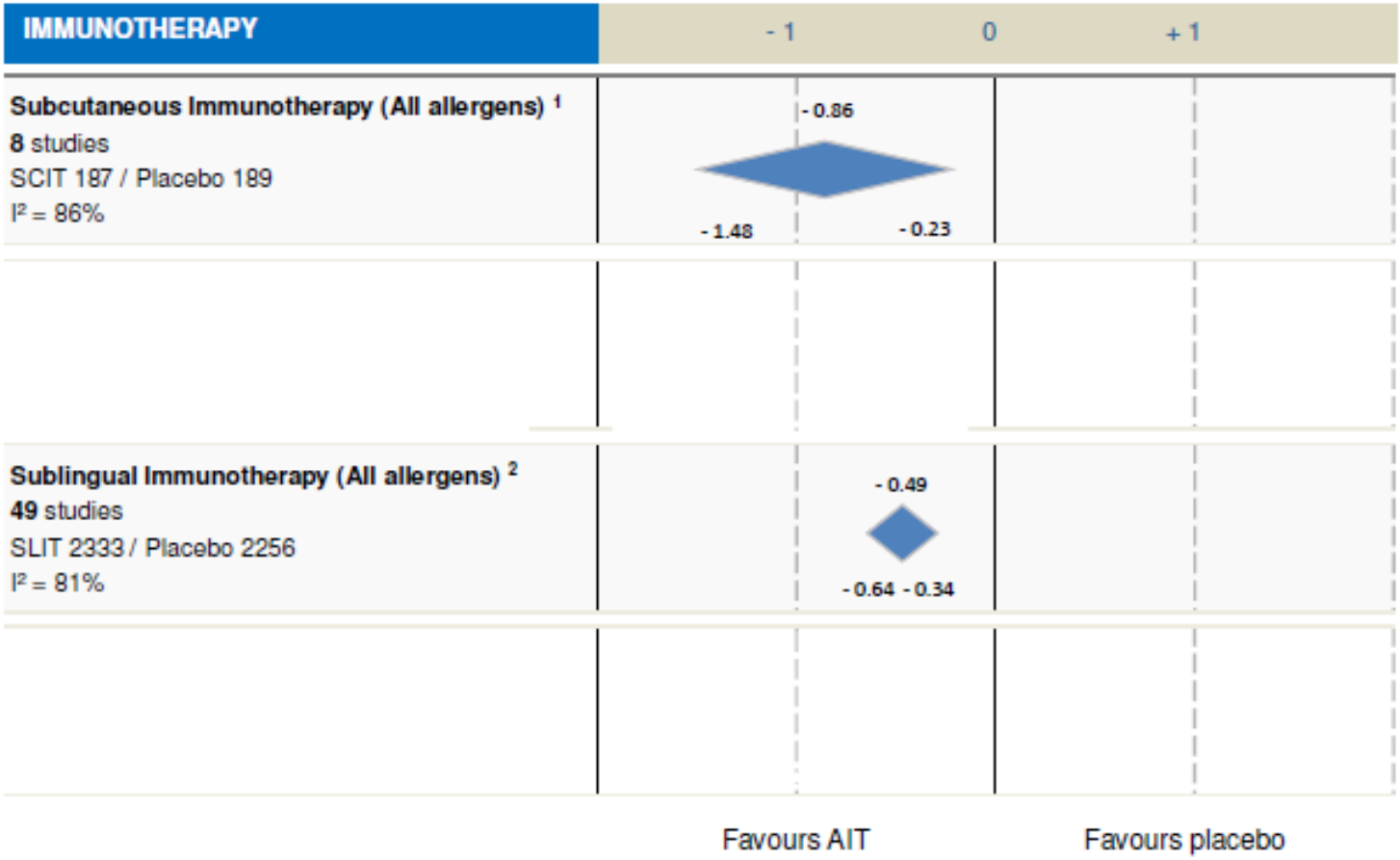
49 studies (2333 active/ 2256 placebo)
SMD (95% CI) = -0.49 (-0.64; -0.34)
p < 0.00001
I^2 = 81%

Radulovic S et al. Cochrane Database Syst Rev. 2010

Sub-analysis for HDM only

9 studies (232 active/ 232 placebo)
SMD (95% CI) = -0.97 (-1.8; -0.13)
p = 0.02
I^2 = 93%

Allergen Immunotherapy for Rhinitis



[1] Calderon MA et al. Cochrane Database of Systematic Reviews 2013, No.: CD007163 [*In press*]

[2] Radulovic S et al. Cochrane Database Syst Rev. 2010 Dec 8;(12):CD002893.

Allergen Immunotherapy for Asthma

SCIT

All allergens

34 studies (727 active/ 557 placebo)
SMD (95% CI) = -0.59 (-0.83; -0.35)
p = <0.00001
I^2 = 73%

Abramson M et al. Cochrane Database Syst Rev. 2010

Sub-analysis for HDM only

12 studies (247 active/ 161 placebo)
SMD (95% CI) = -0.48 (-0.96; 0.0)
p = 0.048
I^2 = 77 %

SLIT

All allergens

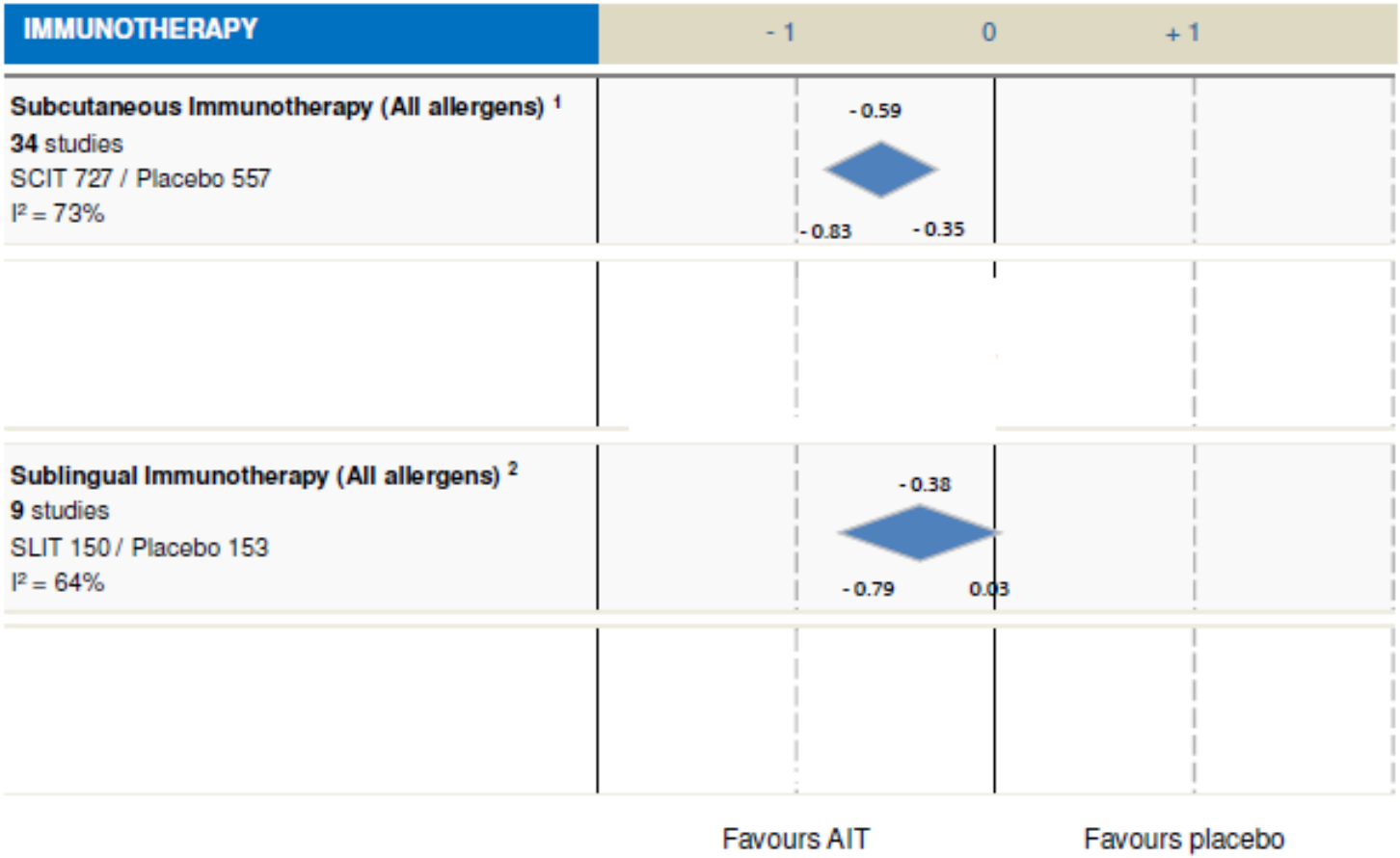
9 studies (150 active/ 153 placebo)
SMD (95% CI) = -0.38 (-0.79; 0.03)
p = 0.07
I^2 = 64%

Calamita Z et al. Allergy 2006

Sub-analysis for HDM only

4 studies (55 active/ 53 placebo)
SMD (95% CI) = -0.54(-1.49; 0.41)
p = 0.27
I^2 = 79 %

Allergen Immunotherapy for Asthma



[1] Abramson MJ et al. Cochrane Database Syst Rev. 2010 Aug 4; (8): CD001186.

[2] Calamita Z et al. Allergy 2006; 61: 1162-72.

Heterogeneity

- **Clinical heterogeneity**
  - Variability in the participants
  - Variability in interventions
  - Variability in outcomes
- **Methodological heterogeneity**
  - Variability in trial design
  - Variability in study quality
  - Variability in allergen extracts
  - Variability in dose schedules
- **Statistical heterogeneity**
  - Due to clinical and/or methodological diversity

New well-powered, well-designed studies using standardised products will provide robust and definitive information regarding optimal dose, regimen duration and post-treatment effect of house dust mite allergen immunotherapy.

Calderon MA et al. Immunol Allergy Clin North Am. 2011; 31(2):

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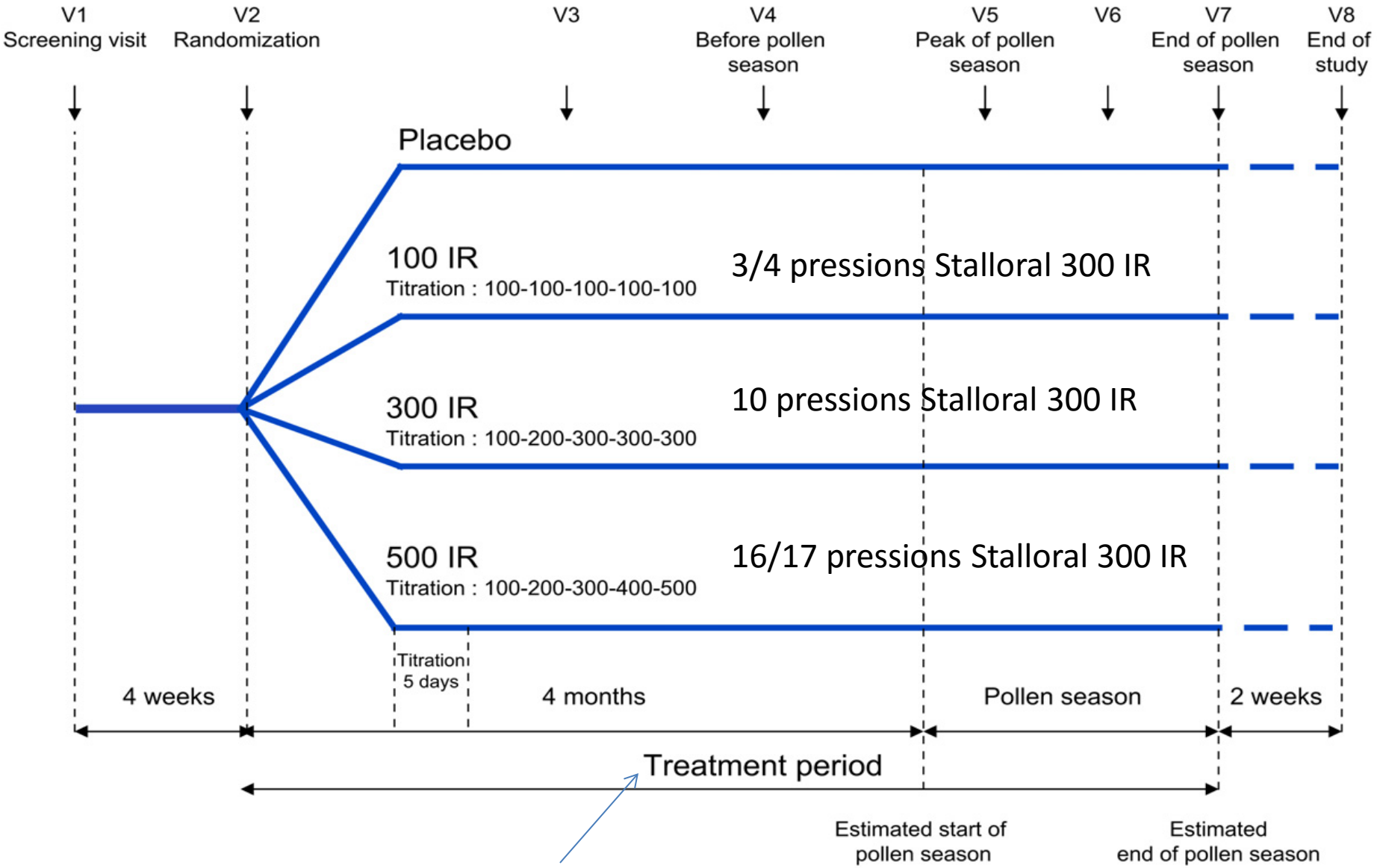
SCIT	First RCT SCIT	SLIT	First RCT SLIT	WHO	ARIA	First Meta SLIT	Large RCT SCIT	First Meta SCIT	Large RCT SLIT	EBM

EBM …mais comment en pratique.

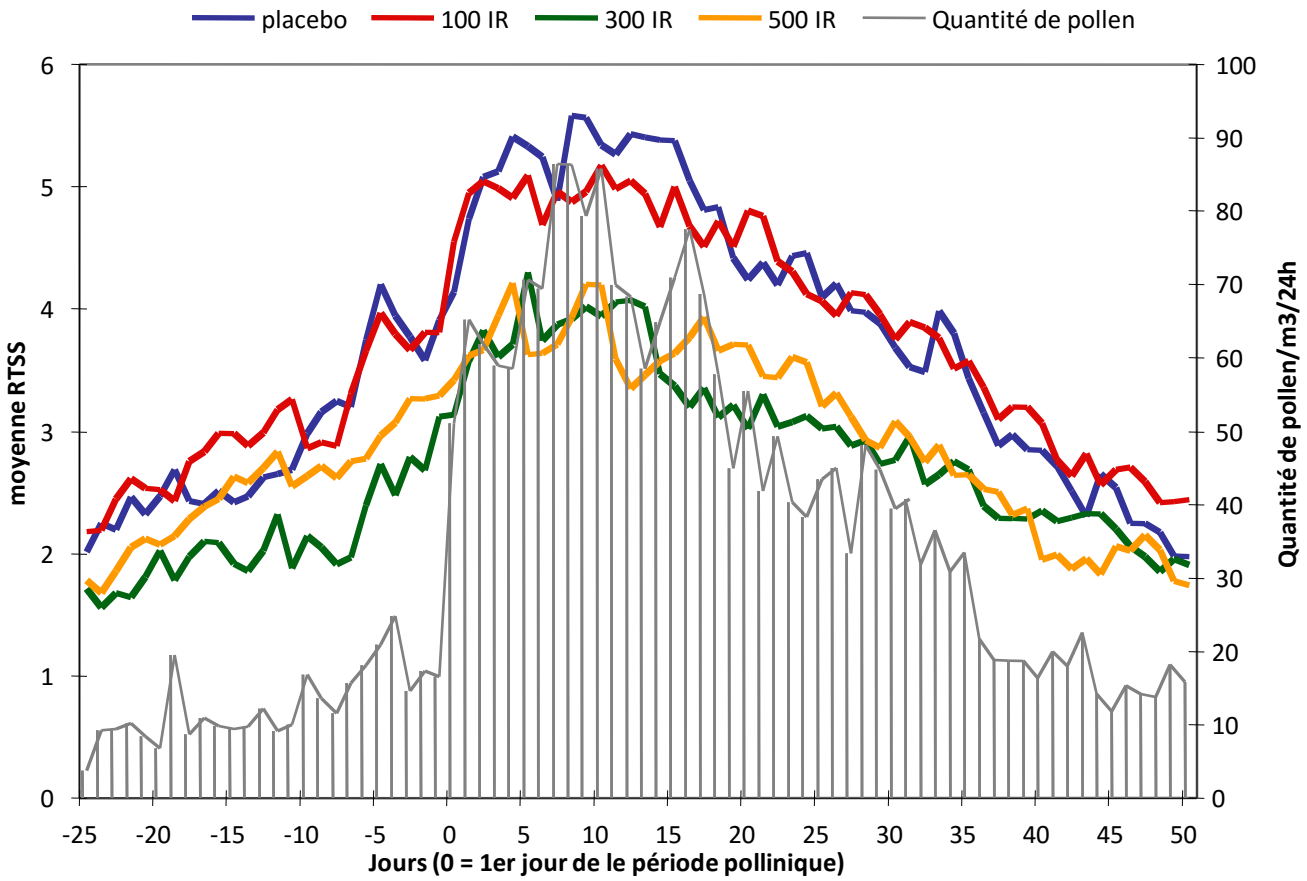
- Quel allergène ?
- Doses ?
- SCIT/SLIT: solution, comprimé ?
- Pré/ Co saisonnier ?
- Tous les jours , 2 ou trois fois par semaine ?
- Combien de temps ?
- Quels bénéfices en pratique ?
- Pour qui ?
- Efficace après combien de mois ?
- Pour quelle durée ?

VO34 , Oralair, 628 adultes



Reference
Didier A *et al*. JACI 2007

Figure 3: Moyenne quotidienne RTSS et niveau de pollen de graminée (2005)



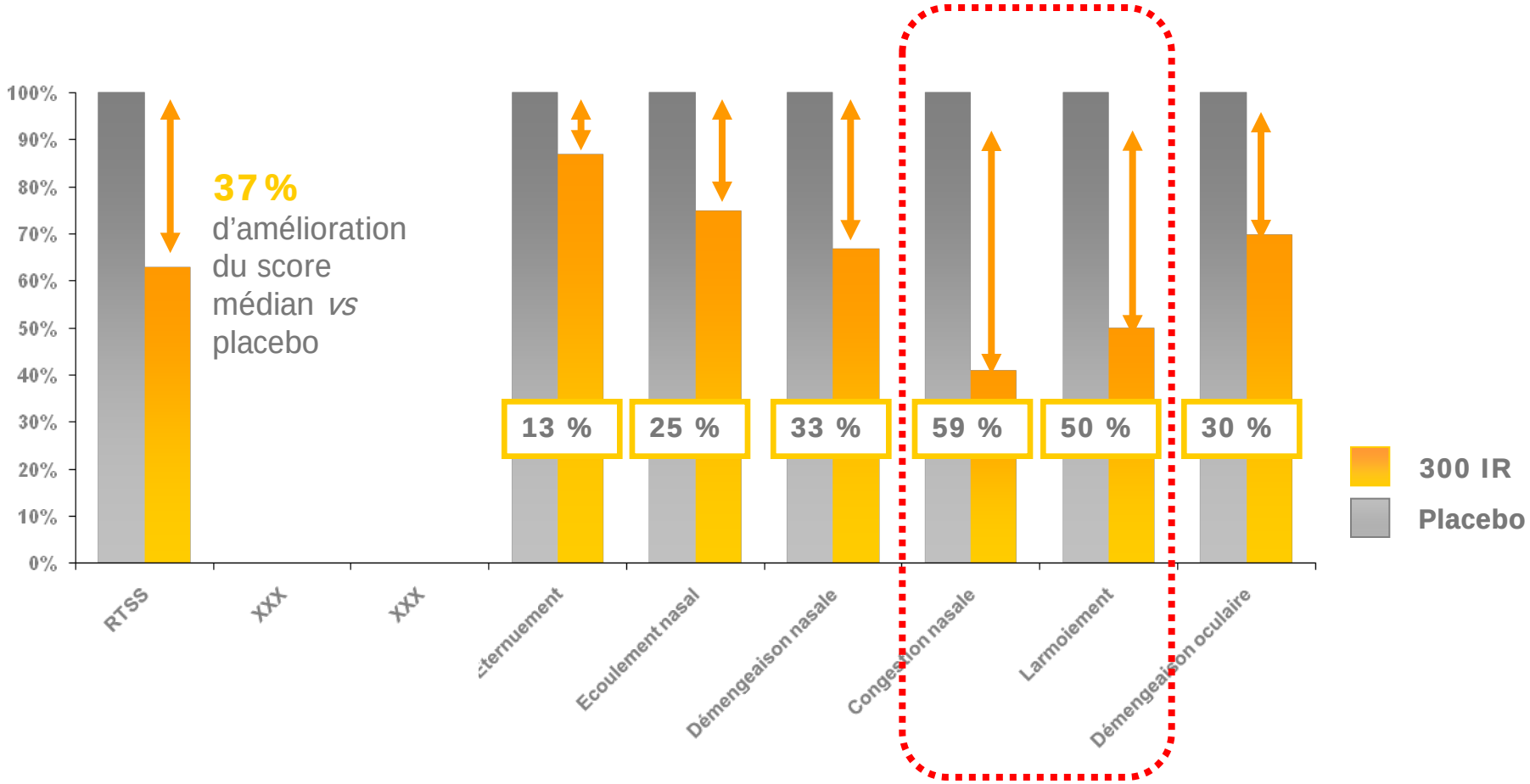
Les scores des moyennes quotidiennes des symptômes sont représentés par une courbe pour chaque groupe de traitement, avec le barème correspondant sur l'axe vertical de gauche.

Les moyennes quotidiennes des quantités de pollen de graminée sont représentées par des lignes verticales et le barème correspondant se trouve sur l'axe vertical de droite.

➲ **Efficacité significative pour les 300 IR et 500 IR, dès le 1er jour et tout au long de la saison pollinique, y compris au pic de pollen**

Reference
Didier A *et al*. JACI 2007

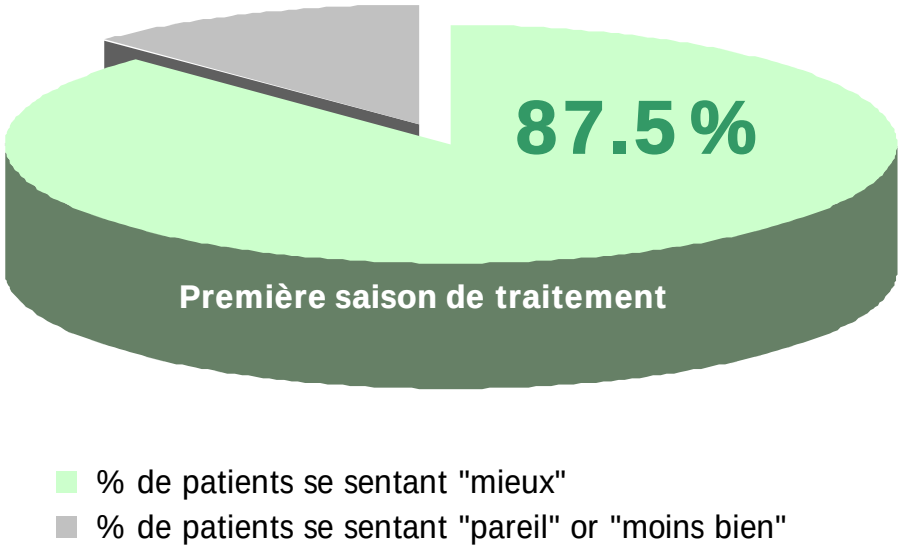
Résultats d'efficacité sur les scores individuels des 6 symptômes



➲ **Les comprimés 300 IR induisent une diminution significative de tous les symptômes, et plus particulièrement de la congestion nasale et du larmoiement**

Reference
Didier A *et al*. JACI 2007

Evaluation globale par les patients



➲ **Dans le groupe 300-IR, environ 9 patients sur 10 se sentent "mieux" dès la première saison de traitement**

Reference
EAACI 2007 Abstract

- Validation de la dose **300 IR** comme la dose optimale
  - Efficacité significative sur le score total symptomatique
  - Moins d'effets secondaires que dans le groupe 500 IR

- Efficacité sur tous les symptômes individuels et particulièrement les plus handicapants: la congestion nasale et les symptômes oculaires

- Efficacité sur tous les sous-groupes de patients : **polysensibilisés** et **asthmatiques**

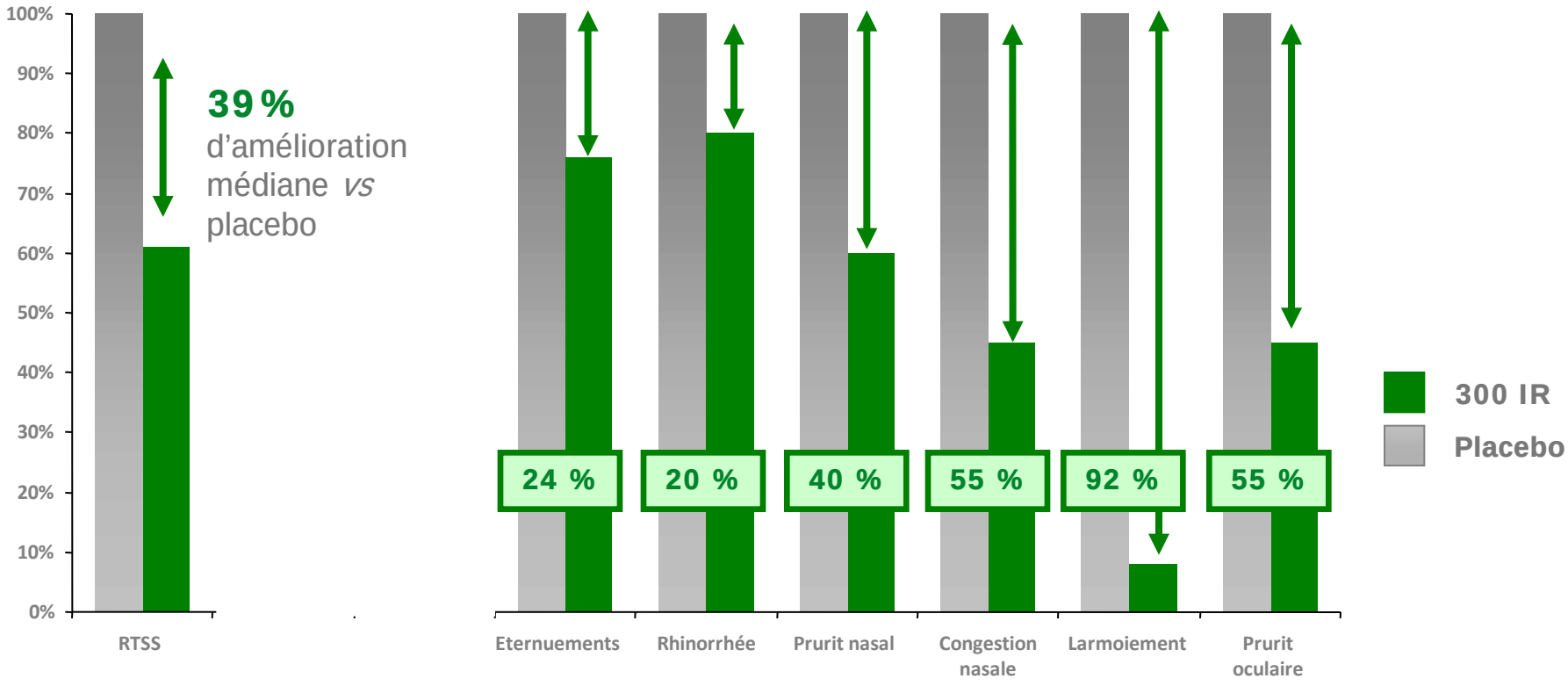
- Effets secondaires en majorité locaux et attendus

Cette étude a permis l'obtention de l'AMM Oralair® chez l'adulte

VO52, Oralair , 278 patients, **5 à 17 ans**
Score des symptômes individuels (ISS,0-3)

RTSS

Scores des symptômes individuels (médiane)

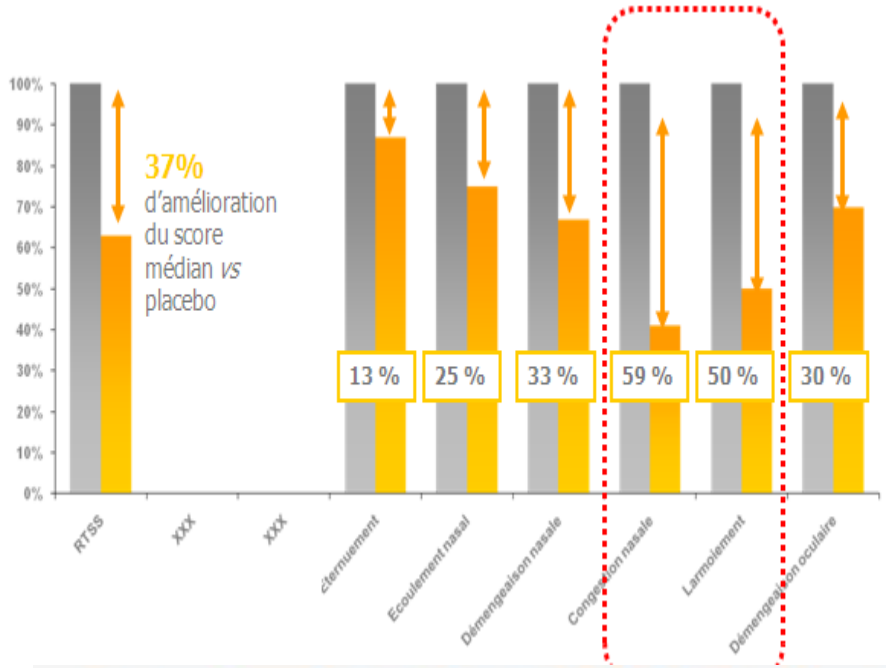


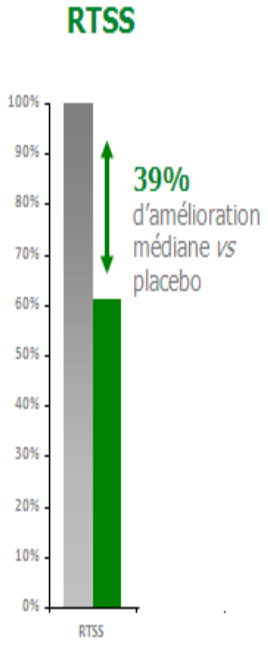
➔ **Diminutions des scores des symptômes individuels comparé à celles du placebo pour les 6 symptômes**

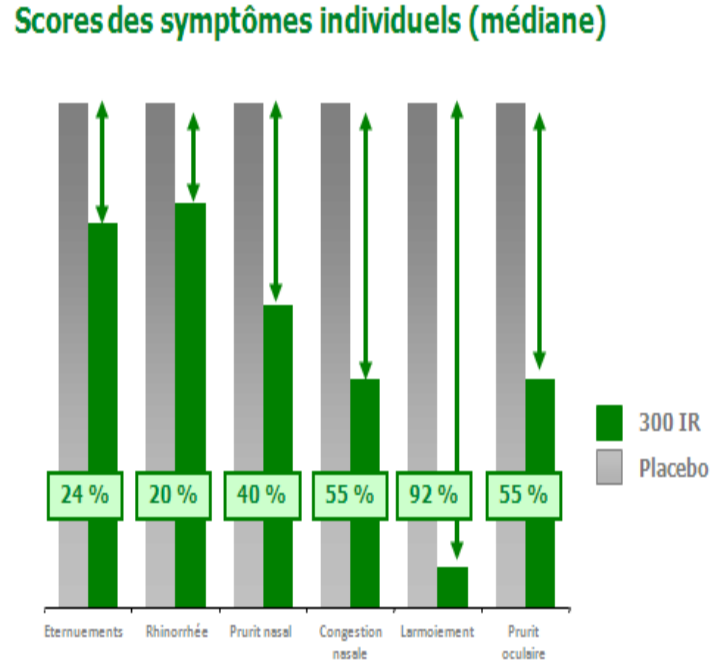
➔ **Amélioration la plus importante pour la congestion nasale et pour les symptômes oculaires**

Reference

Wahn JACI 2008 ; internal data







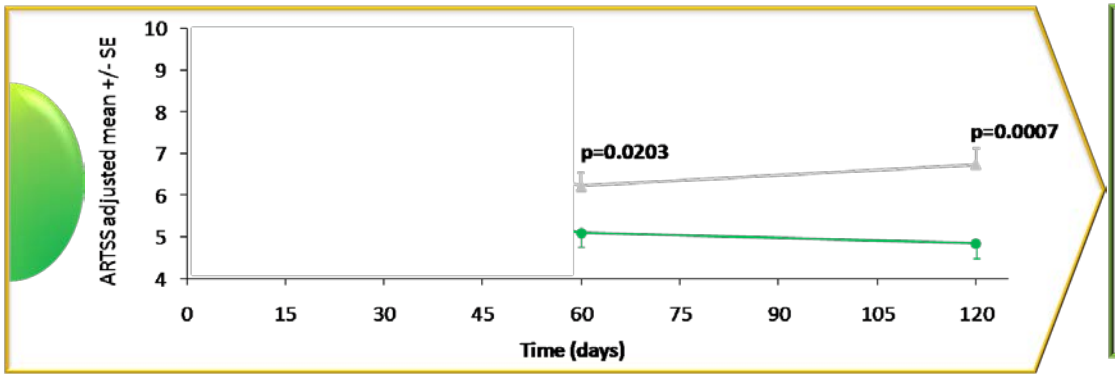
An evaluation of data on the relative clinical impact of sublingual allergen immunotherapy tablets and symptomatic medications in grass-pollen-induced allergic rhinoconjunctivitis

Devillier P.[1], Dreyfus J.-F.[1], Demoly P.[2], Didier A.[3], de Beaumont O.[4], Calderon M.C.[5]

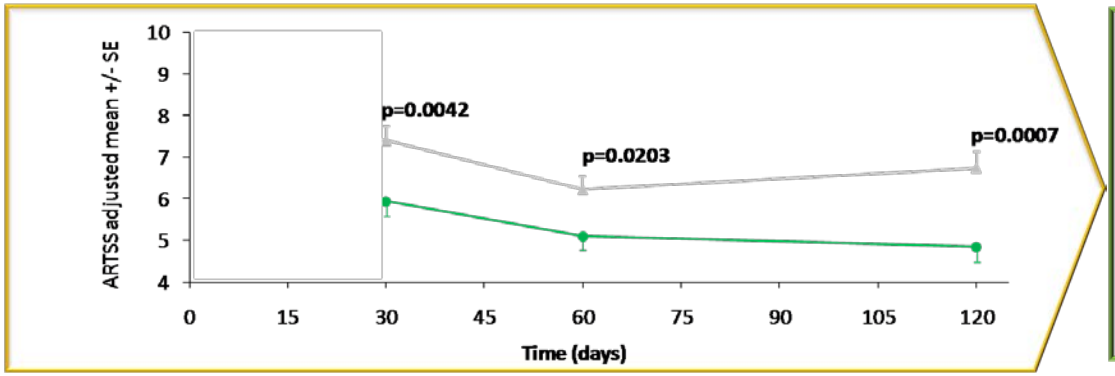
Conclusion: Despite the presence of methodological factors in clinical trials that may lead to underestimate allergen immunotherapy effect size, grass pollen SLIT tablets appears to have a greater RCI than second-generation H1-antihistamine and montelukast and much the same RCI as nasal corticosteroids in poorly controlled patients with moderate-to-severe SAR.

Onset of action ?

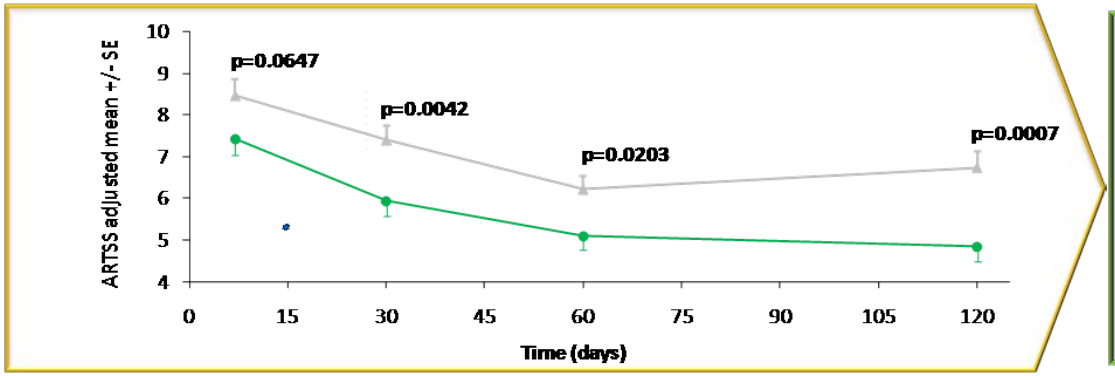
ORALAIR
Etude VO56 en **chambre**
Horak 2009



At 2 months of treatment a significant improvement is observed in patients treated with Oralair® vs. placebo



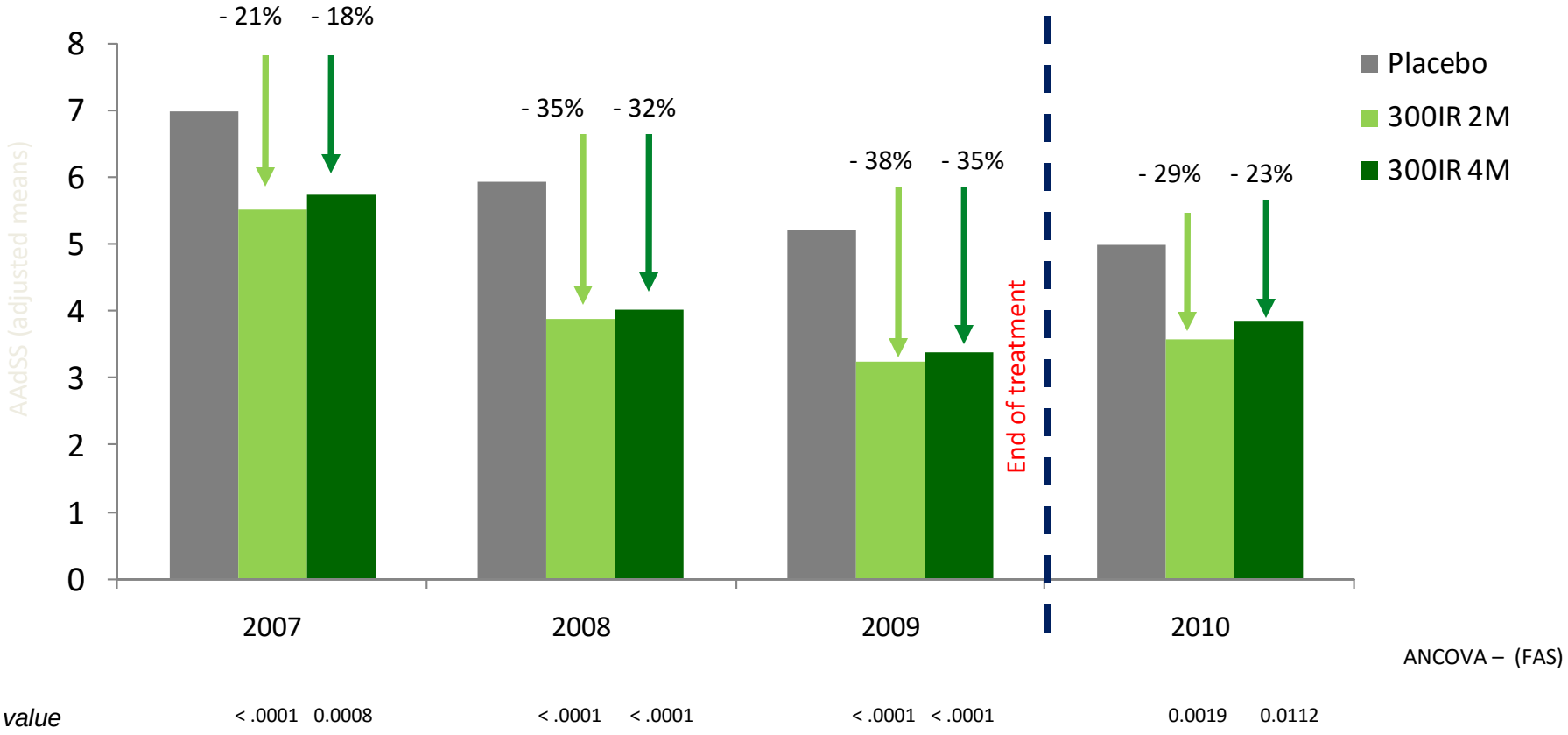
From the end of the 1st month of treatment, a significant ARTSS improvement is observed in the Oralair® group vs. placebo



At the end of the 1st week of treatment a trend for symptom improvement was seen in the active group vs. placebo, although not statistically significant yet

Primary efficacy endpoint: AAdSS Pollen season - years 1 to 4

Étude long terme V053 (2 mois vs 4 mois) ; étude Didier, 2013

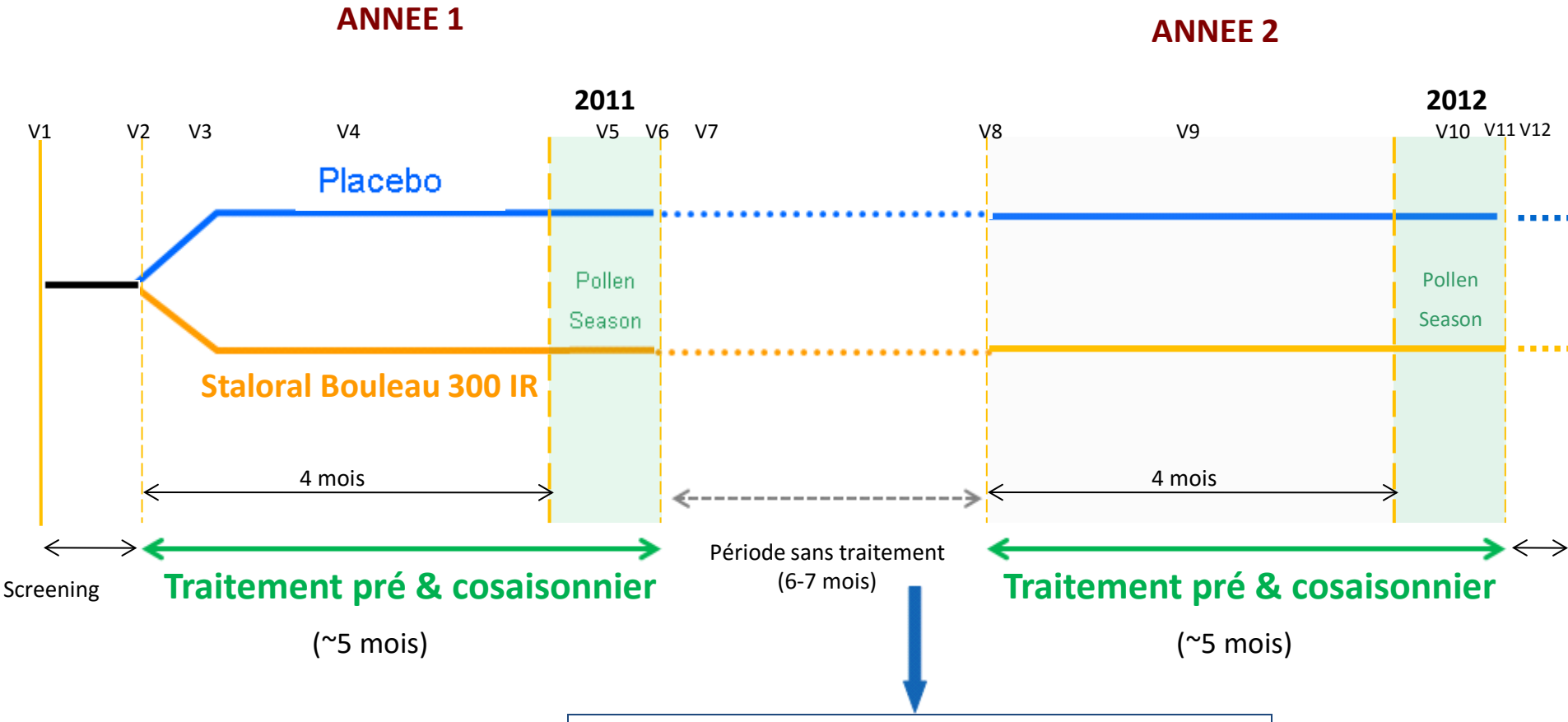


- From the first season on, significant difference between active and placebo
- Continued efficacy following **cessation** of the treatment

VO68 – Bouleau 2013

Produit	STALORAL extrait de pollens de bouleau vs Placebo
Dose d'entretien	300 IR/jour **<u>10 pressions</u>**
Population	Adultes avec rhinoconjonctivite allergique induite par le bouleau
Taille planifiée de l'échantillon	544 patients randomisés (272/bras)
Pays Sites	11 pays: CZ, DK, Est., Fin., FR, G., Lat., Lit., Pol., SK, S. 56 sites
Coordinateur	Prof. M. Worm (Berlin, Allemagne)

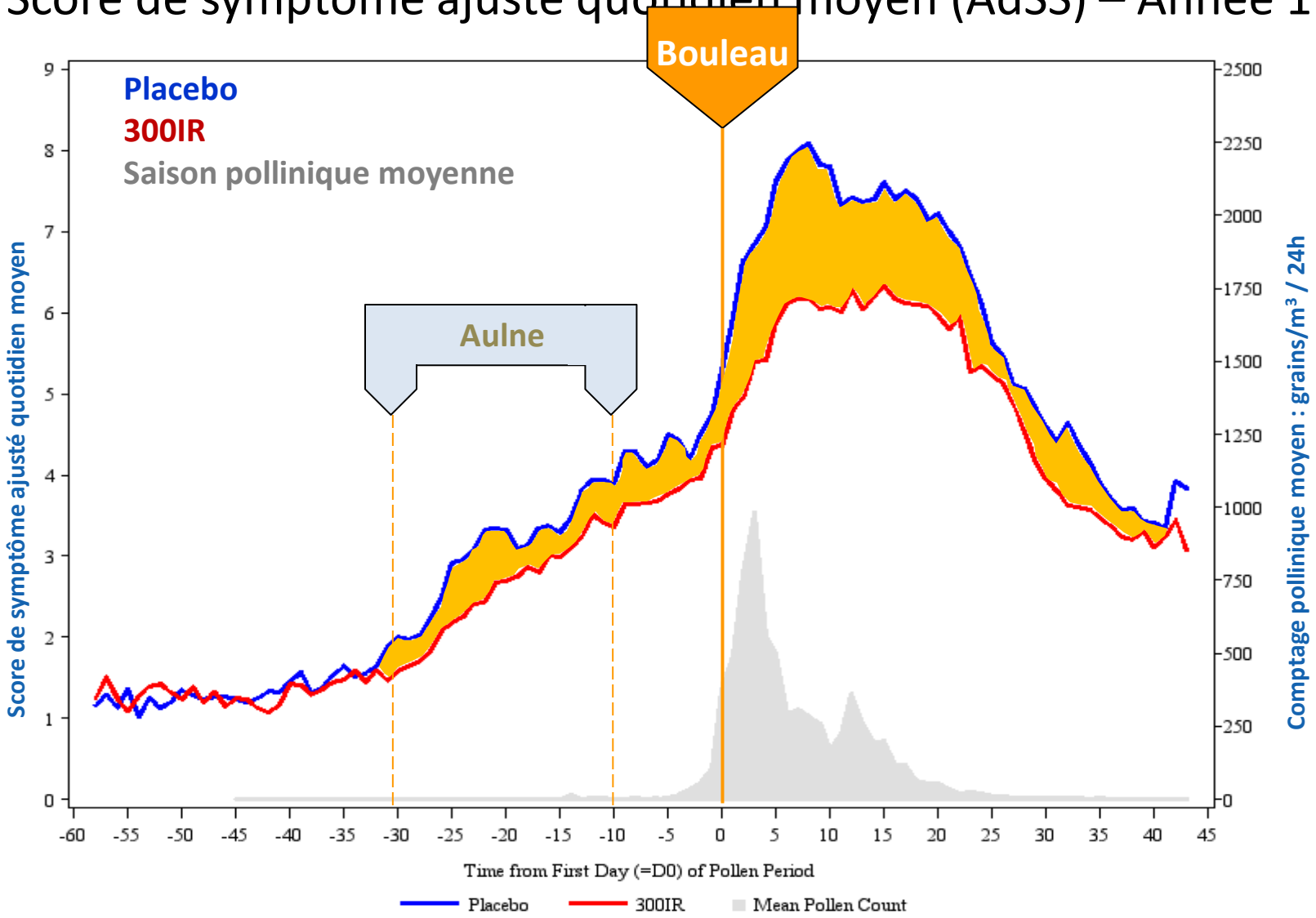
VO68 – Design de l'étude



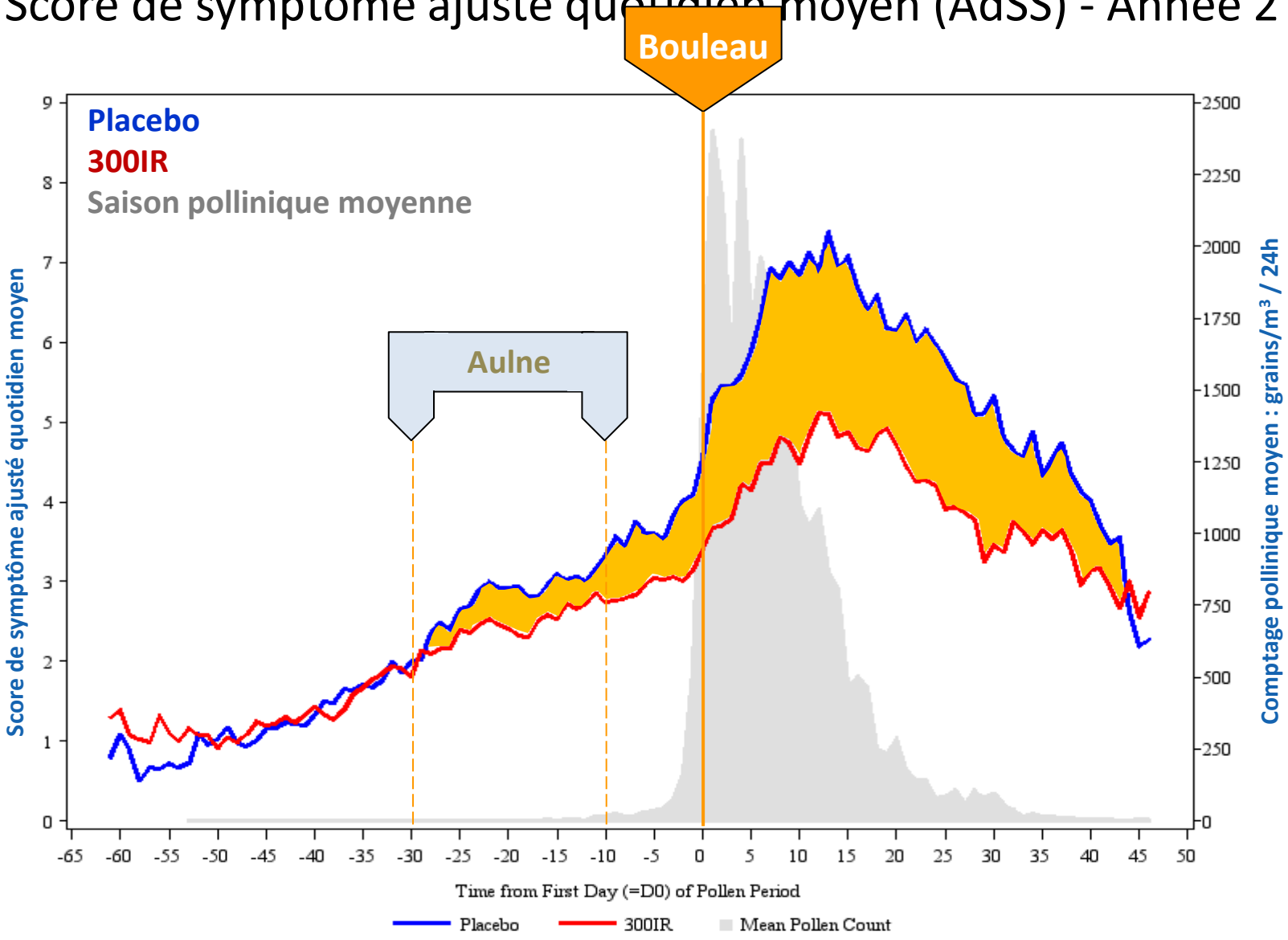
DSMB meeting

- Revue des données d'efficacité et de sécurité
- Go decision pour l'année 2

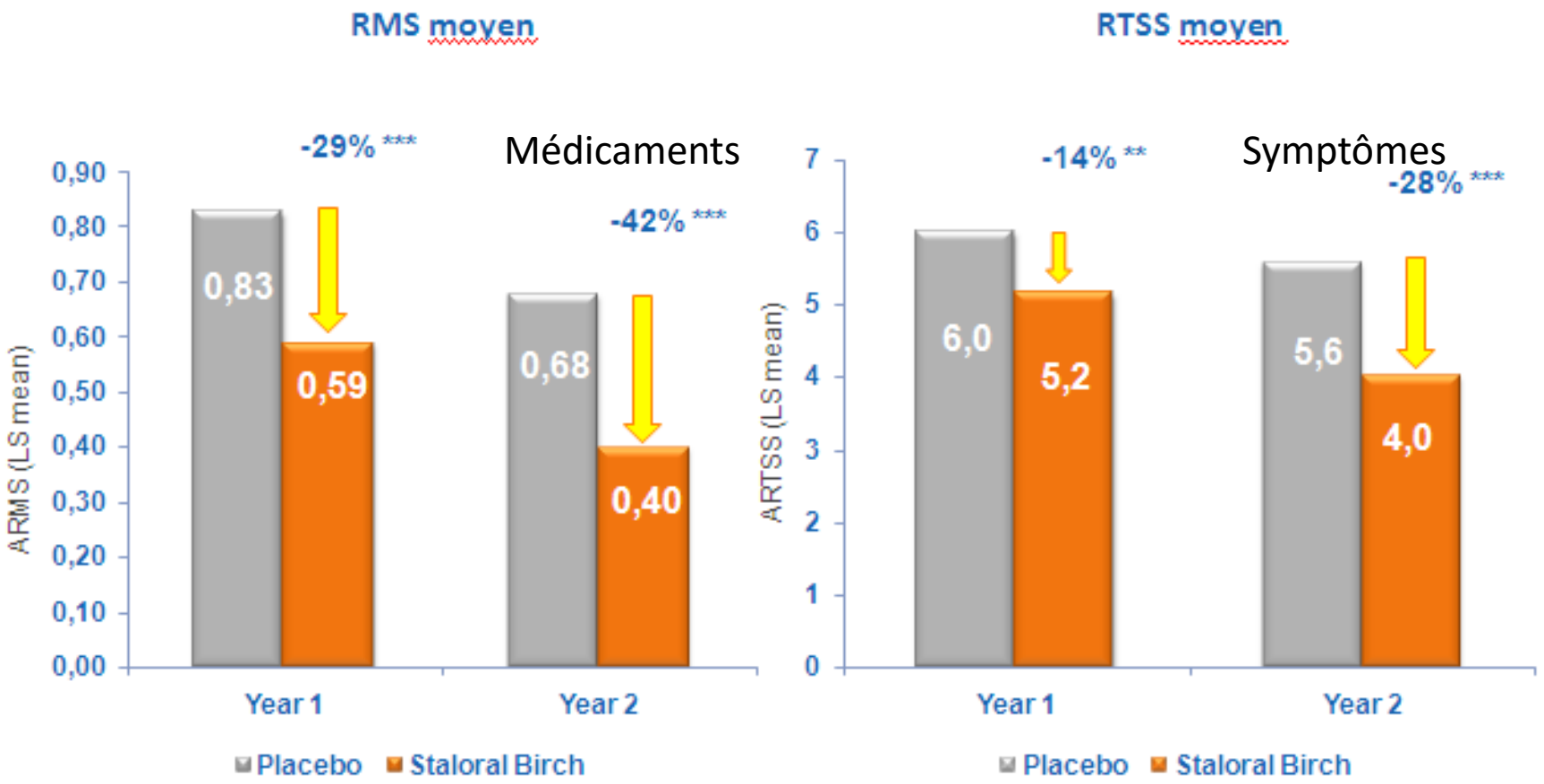
Score de symptôme ajusté quotidien moyen (AdSS) – Année 1



Score de symptôme ajusté quotidien moyen (AdSS) - Année 2



ARMS & ARTSS – Période pollinique – FAS

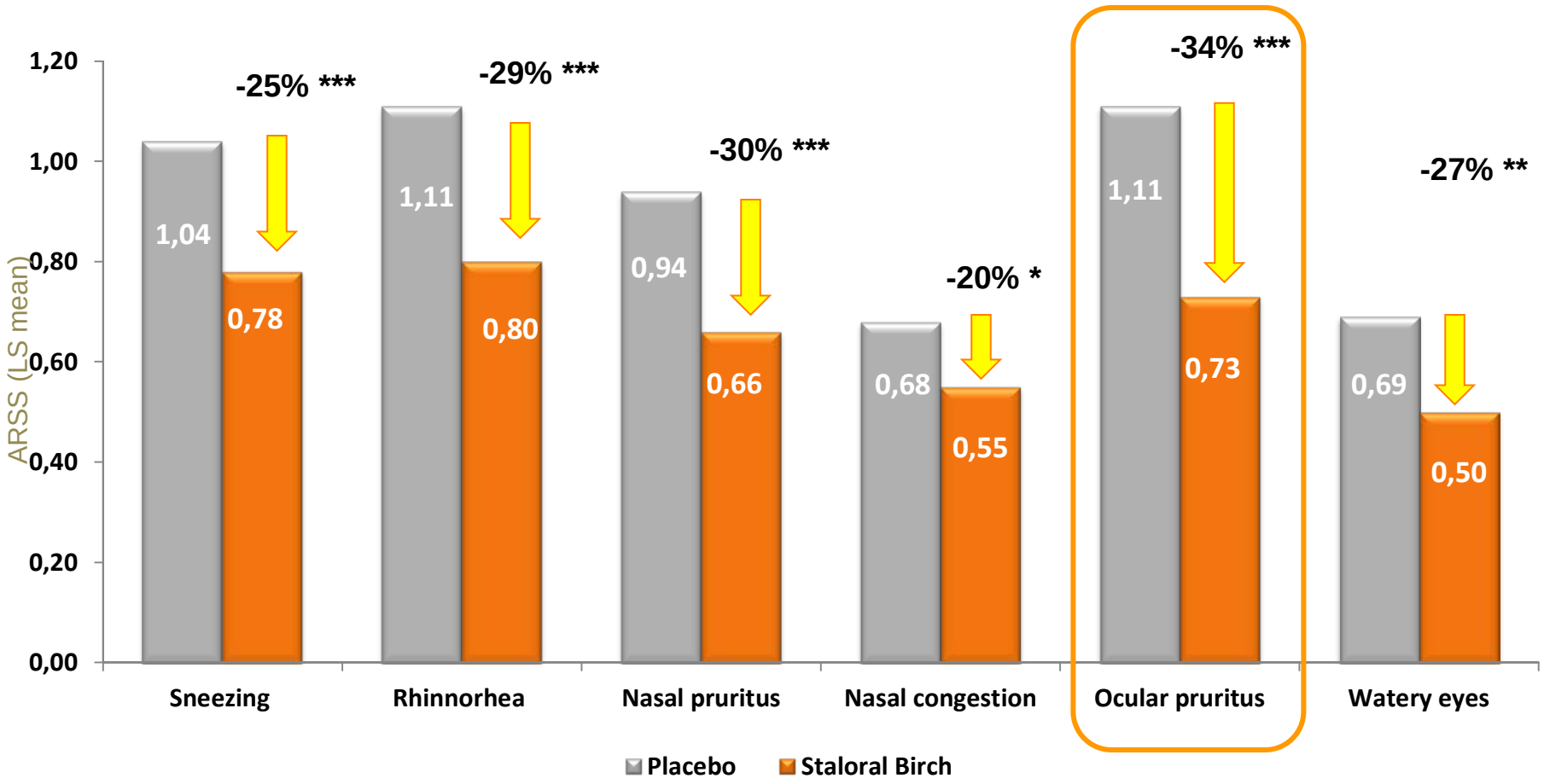


Diminution marquée (de 42%) du score médicamenteux et du score symptomatique total (de 28%) à la fin de la saison 2.

**: p<0.01, ***: p<0.001

Scores moyens des symptômes de rhinoconjonctivite

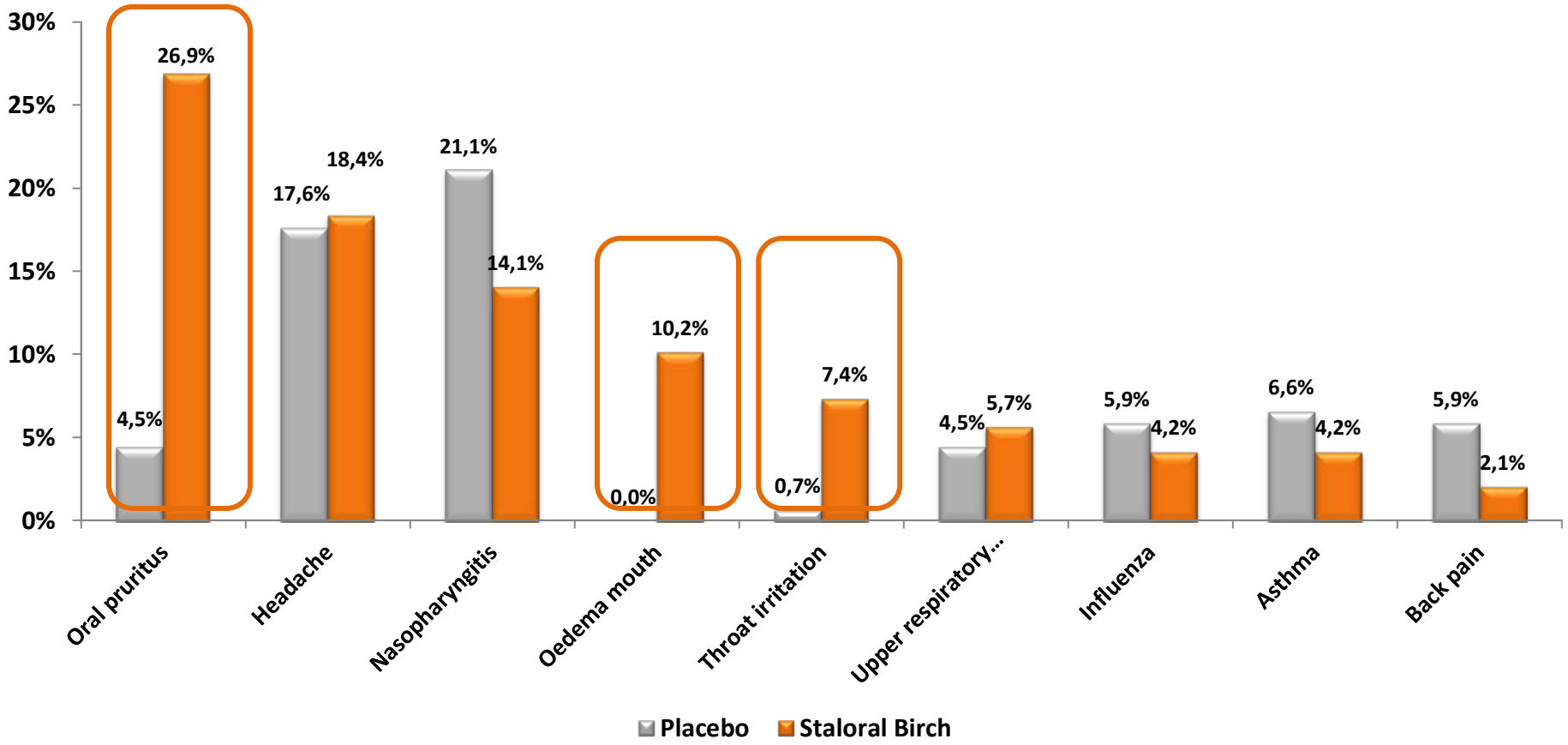
Scores des symptômes individuels (ARSSs) – Année 2 Période pollinique – FAS



Réduction marquée de **tous les symptômes** et en particulier des **symptômes oculaires** à la fin de la saison 2**.**

*: p<0.05; **: p<0.01; ***: p<0.001

TEAE (≥ 5%) les plus fréquents – Global - Safety Set



Le profil de sécurité est en ligne avec ce que l'on attend de Staloral, avec principalement des effets secondaires locaux.

VO68 – Conclusions générales

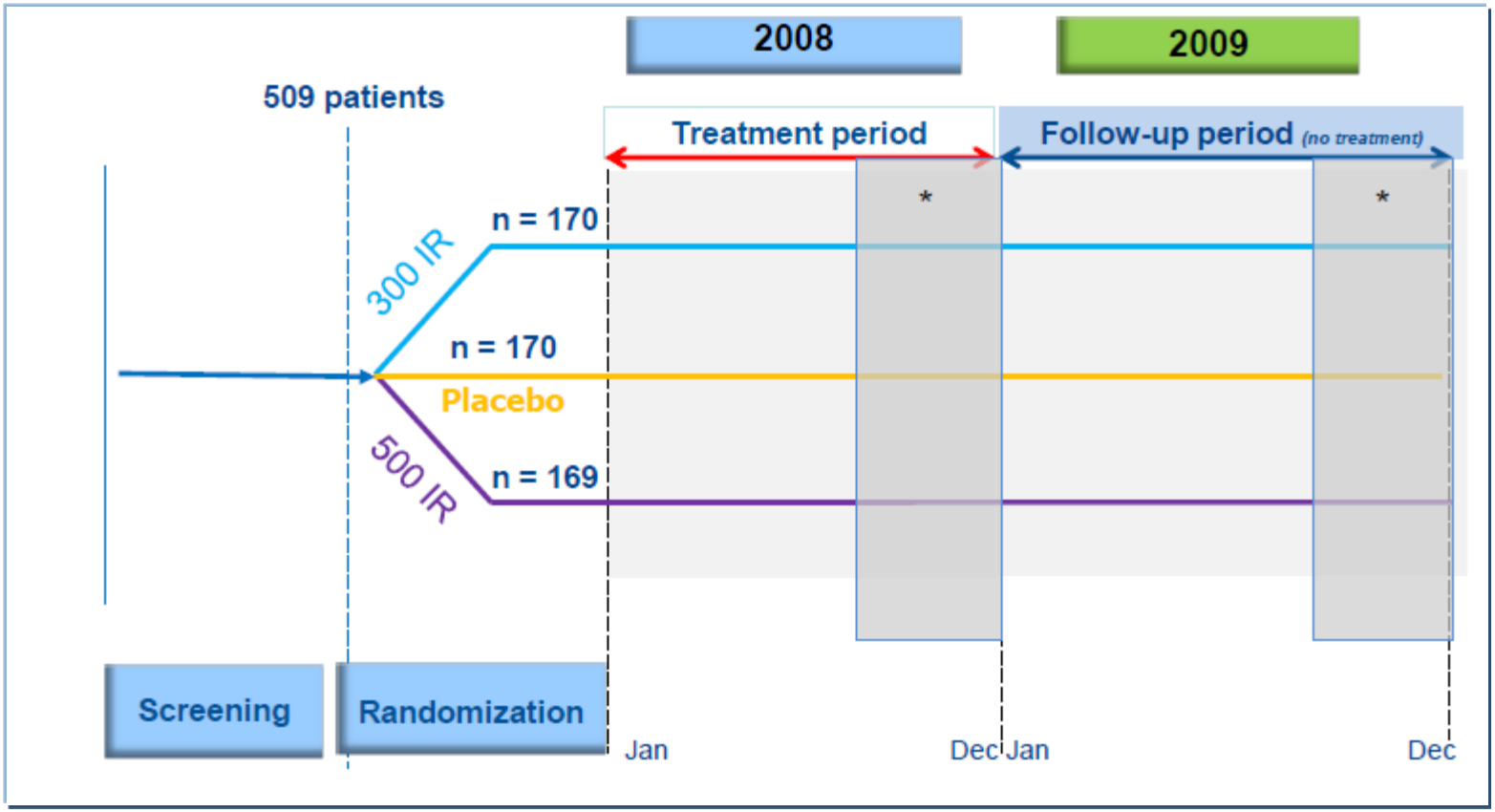
- L'analyse primaire de l'efficacité montre une différence hautement significative entre Staloral® et le placebo: **efficacité soutenue de -31% en Année 2**

- Les données de sécurité montrent une différence attendue entre le groupe actif et le placebo principalement avec des réactions au site d'administration

Un traitement quotidien en pré&cosaisonnier de Staloral® Bouleau 300 IR sur 2 ans est efficace et bien toléré

Etude VO57- RA – Actair Derm pteron /Derm far

509 patients randomisés Europe multicentrique



*** Période d'évaluation du critère primaire pour les deux années: 1 Oct – 31 Dec**

Critère primaire d'efficacité – AAdSS

Average Adjusted Symptom Score

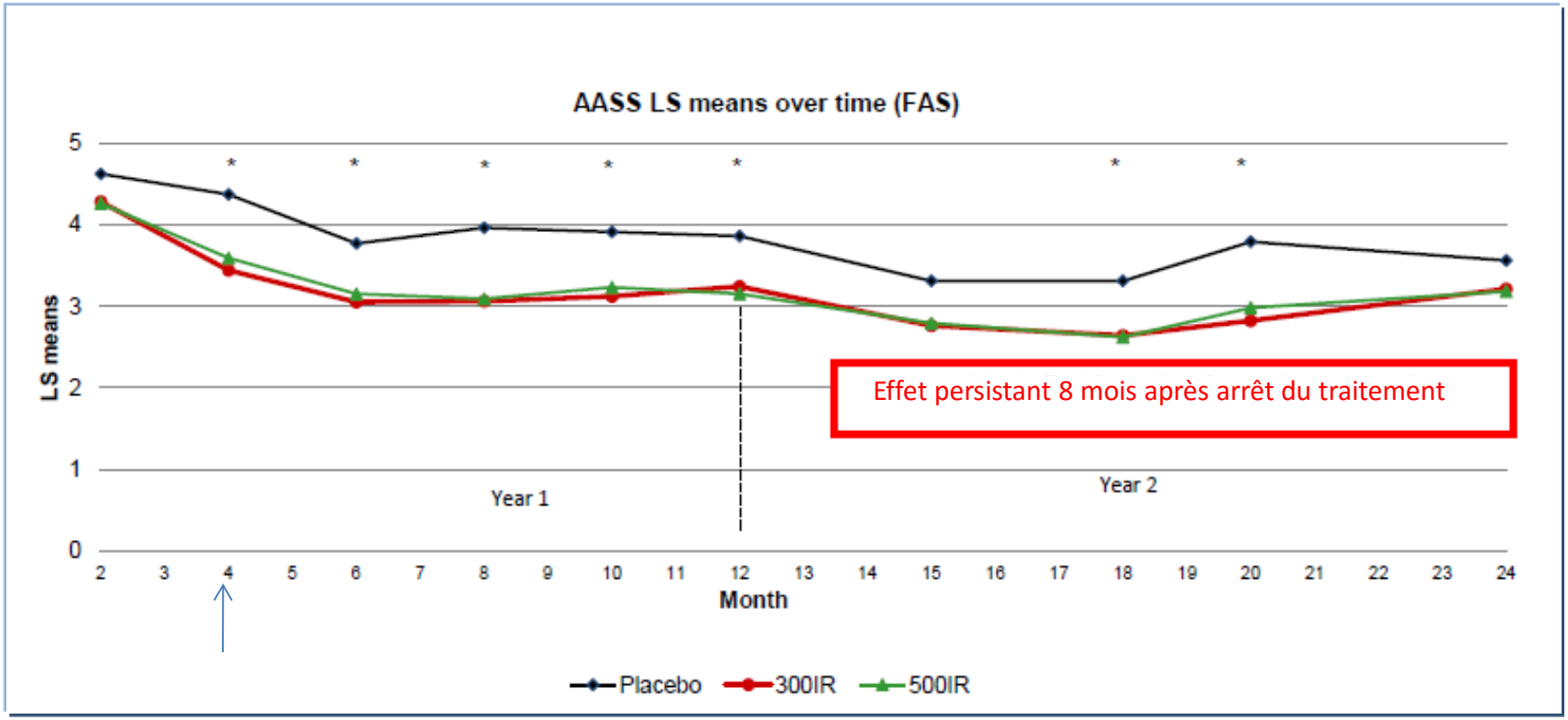
	Treatment	AAdSS Means	LS Means Difference [95% CI]	*p-value*	LS Means Difference [95% CI]
Primary period (1 Oct- 31 Dec 2008)	Placebo	3.81			
	500 IR vs Placebo	3.21	**- 0.78 [-1.34;-0.22]**	**0.0066**	**- 20.2%**
	300 IR vs Placebo	3.14	**- 0.69 [-1.25;-0.14]**	**0.0150**	**- 17.9%**

La différence relative vs. placebo est de 20.2% pour le groupe 500IR et 17.9% pour le groupe 300 IR

✓Ces différences sont cliniquement significatives

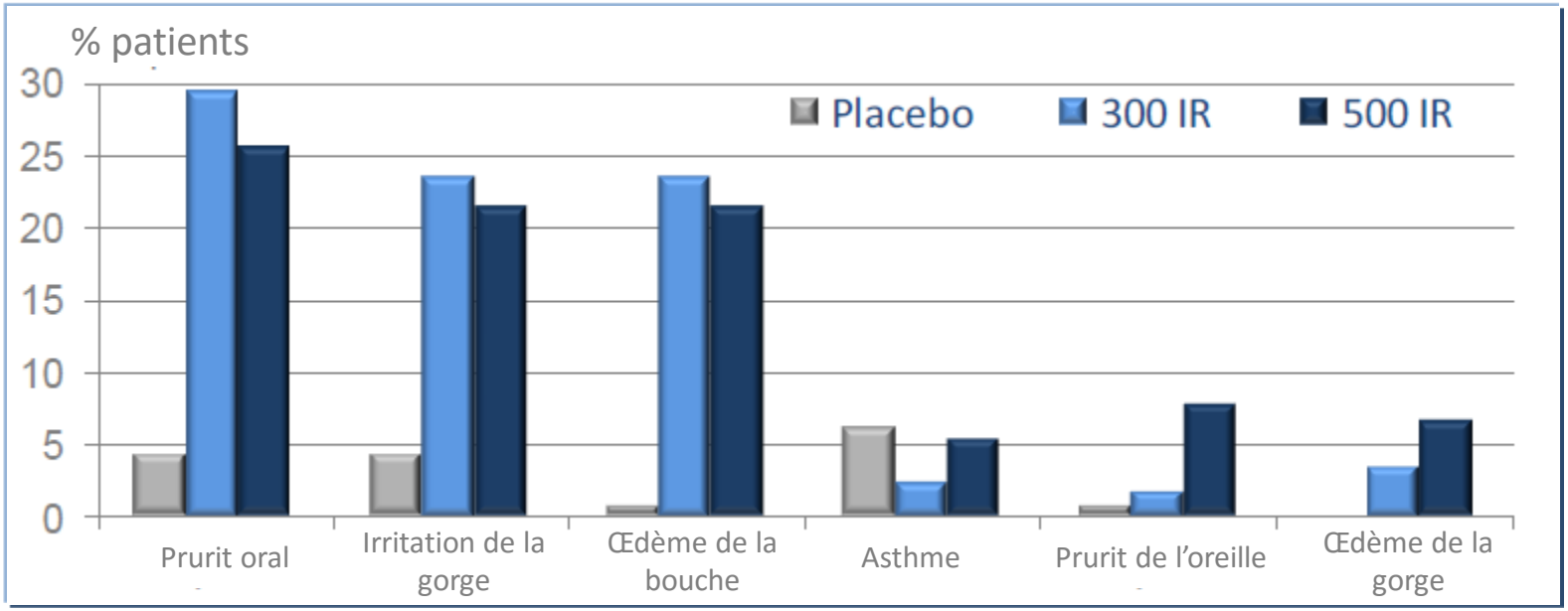
✓Le statut de sensibilisation (mono- vs. polysensibilisés) n'a pas impacté l'efficacité des résultats

AAdSS – Années 1 et 2
Délai d'action et effet post-traitement



Une efficacité significative à partir du **4ième mois**, maintenue tout au long de la phase de traitement (année 1) avec un effet persistant jusqu'à 8 mois après l'arrêt du traitement

Effets indésirables survenant au cours du traitement (≥ 5% dans les groupes traités)



Aucun cas de choc anaphylactique ou d'anaphylaxie

✓Aucun patient n'a reçu de l'adrénaline

✓Les effets indésirables survenus au cours du traitement les plus fréquents étaient les réactions au site d'administration

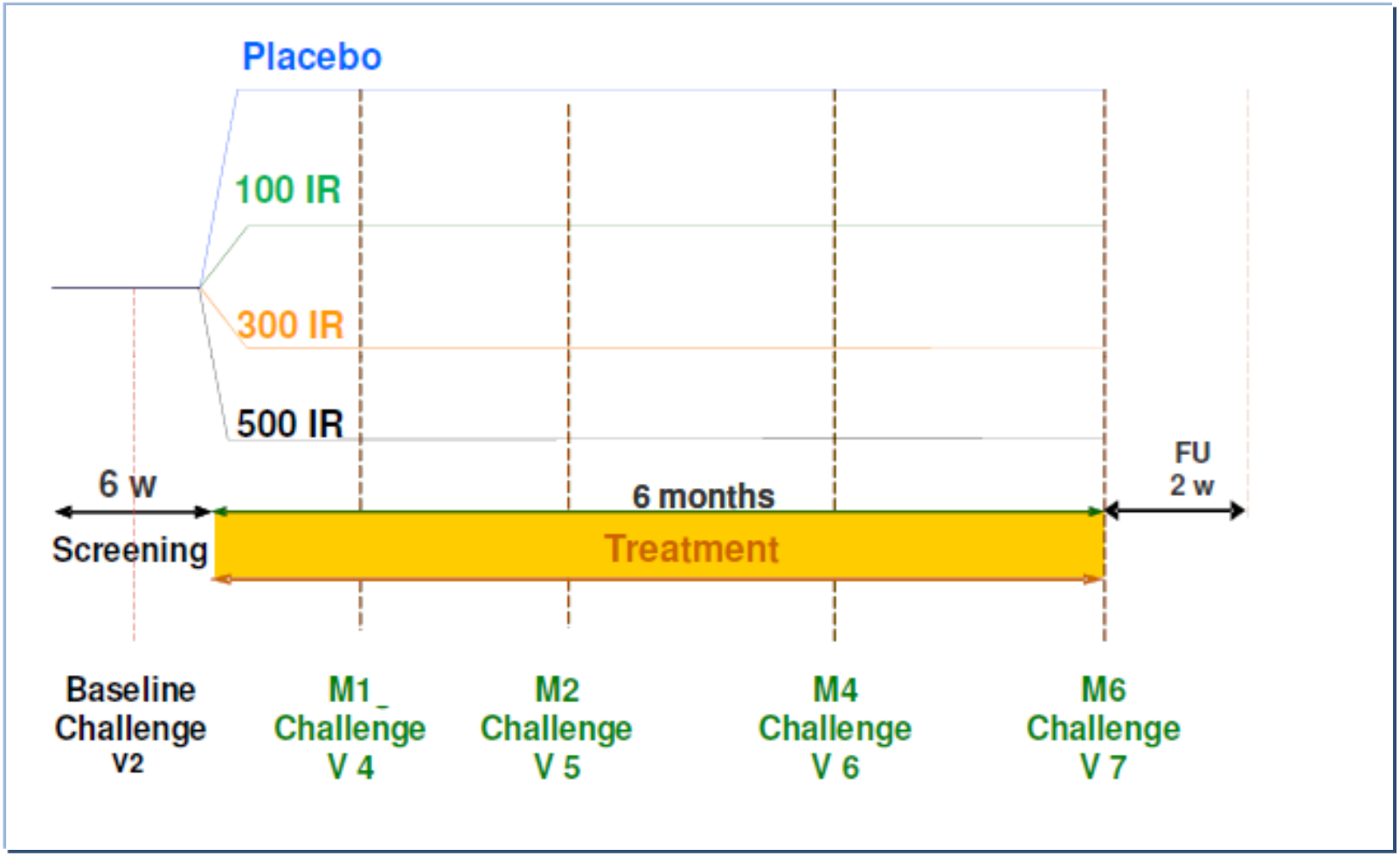
Etude VO57- RA – Actair Derm pteron /Derm far

Première étude qui démontre l'efficacité d'un comprimé sublingual au acariens dans la Rhinite Allergique

- ✓ Bénéfice additionnel dans le groupe **500IR**
  - ✓ 1C= 16/17 pressions Stalloral 300 IR
- ✓ Efficacité à partir du 4ième mois de traitement
- ✓ Effet persistant 8 mois après l'arrêt du traitement

Actair VO676-RA – Derm pteron /derm far

2010 – 2012 355 patients Toronto



VO67 Study: HDM SLIT Tablets in Allergic Rhinitis

Environmental Allergen Exposure Chamber

- Turbulent airflow delivered a constant flux of *D. pteronyssinus*
- Concentration of 10-120 mcg/m^3 of *Der p1*
- 4-hour duration, dose was continuously monitored
- Patients scored symptoms every 15min for 2 hrs, then every 30min for 2 hrs

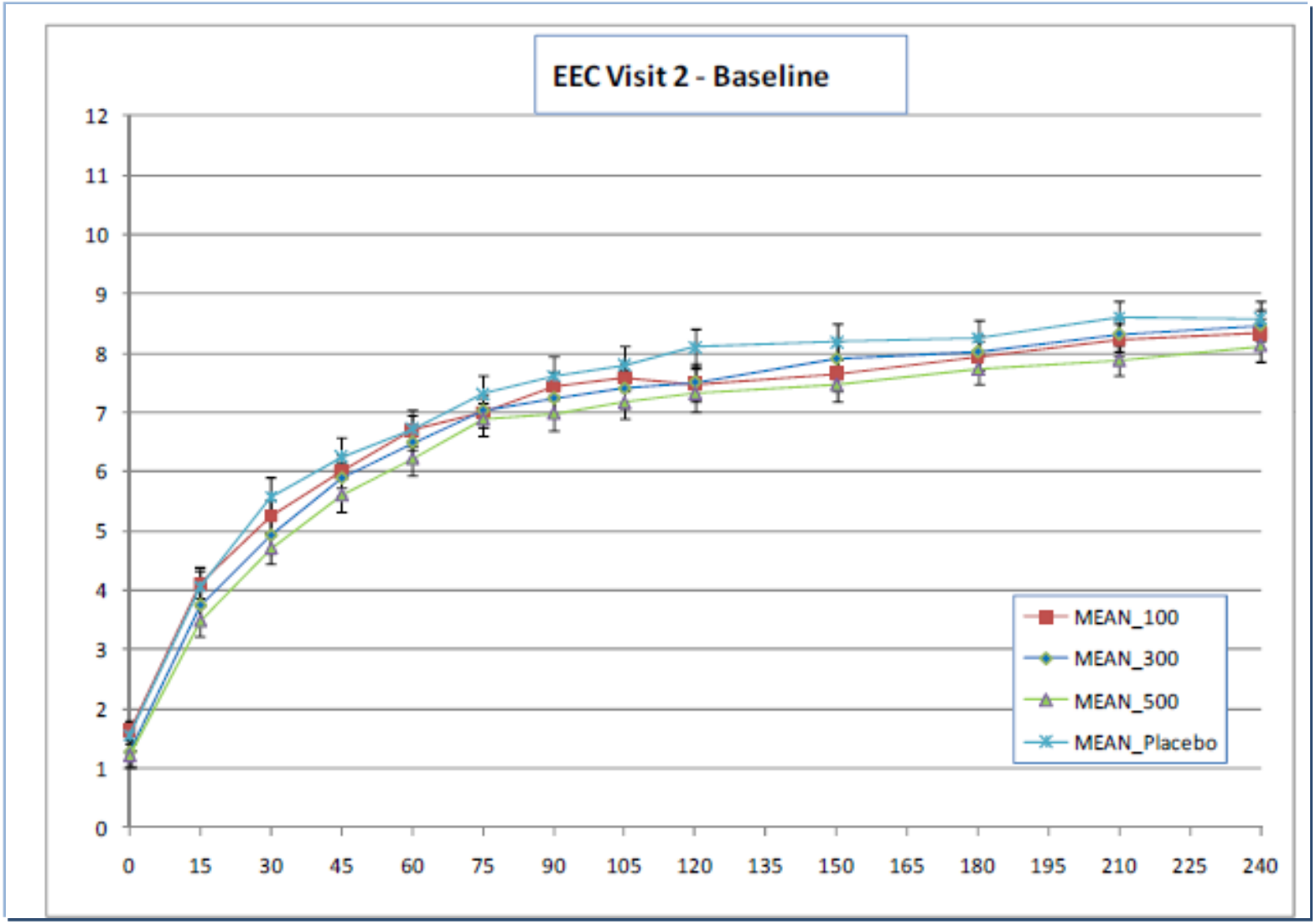
VO67 - Analyse d'efficacité primaire (FAS)

ANCOVA – Changement par rapport au baseline de l'AUC du score total de rhinite de 0 à 4h (ChBL AUCRTSS 0-4h) après 6 mois de traitement

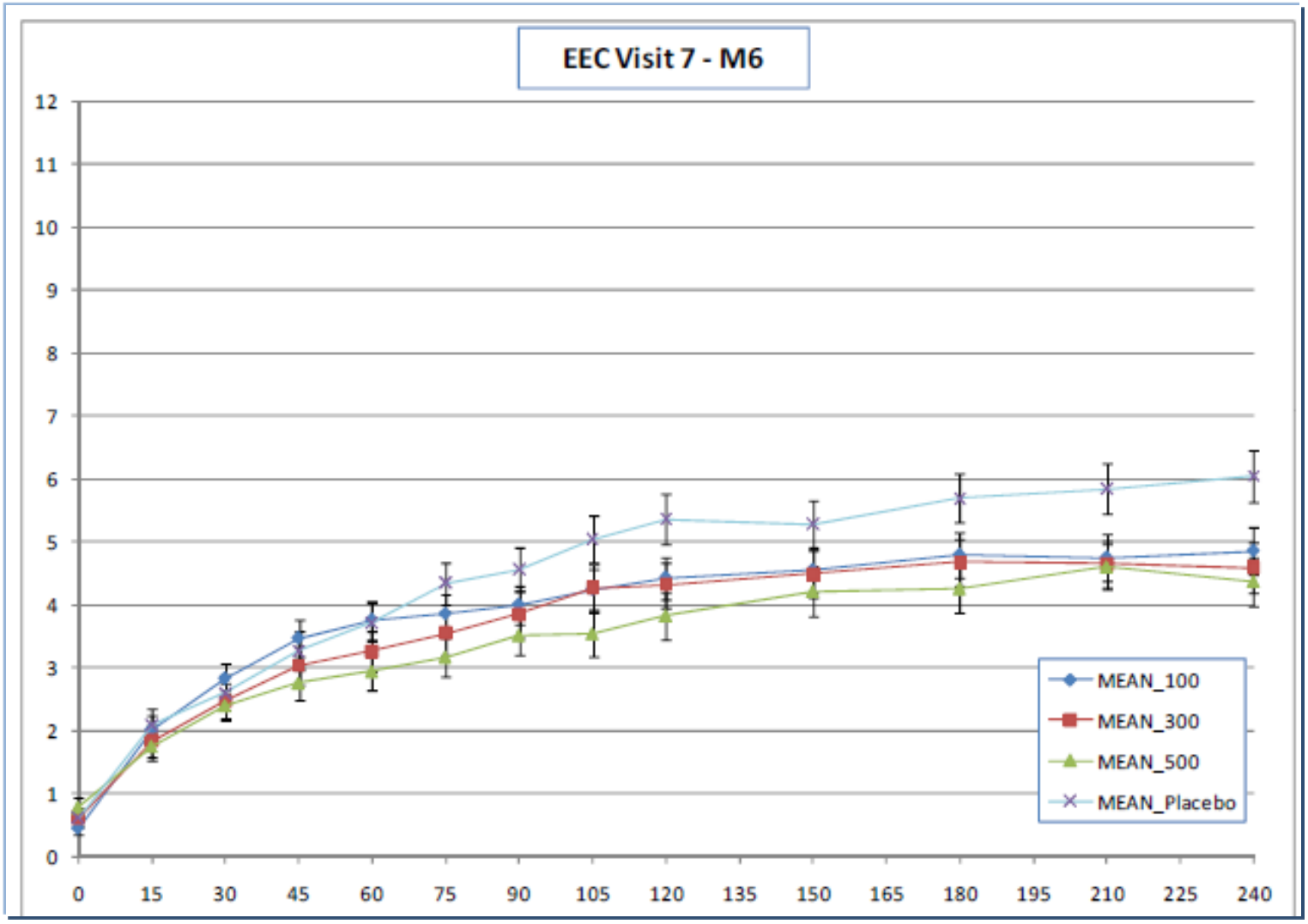
Ch_{BL} $AUC_{RTSS\ 0\text{-}4h}$					Difference versus Placebo			
Treatment	n	Miss.	LS Mean	SE	LS Mean difference	95% CI	p-value	Relative LS Mean difference
500 IR	70	23	-795.6	69.88	-198.2	[-389.6 ; -6.6]	**0.0427**	33.2%
300 IR	68	18	-769.2	70.66	-171.8	[-363.9 ; 20.2]	0.0793	28.8%
100 IR	75	14	-715.8	67.26	-118.4	[-305.9 ; 69.0]	0.2147	19.8%
Placebo	75	12	-597.4	67.40				

CI: Confidence interval ; SE: Standard error; LS: Least Squares; ANCOVA: Analysis of Covariance; Miss.: number of missing values

RTSS au cours du challenge au baseline



RTSS au cours du challenge après **6 mois de traitement**



VO67 – Effets indésirables

Description	500 IR (N = 93) n	(%)	300 IR (N = 86) n	(%)	100 IR (N = 89) n	(%)	Placebo (N = 87) n	(%)
At least one TEAE	87	(93.5)	78	(90.7)	86	(96.6)	72	(82.8)
At least one drug-related TEAE	66	(71.0)	59	(68.6)	60	(67.4)	38	(43.7)
At least one serious TEAE	2	(2.2)	1	(1.2)	1	(1.1)	0	(0.0)
At least one serious drug-related TEAE	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)

Related (Investigator assessment): Relationship to IP = missing, or 'Possible', 'Probable/Likely' or 'Highly probable/Certain'

✓TEAE: effets indésirables survenant au cours du traitement

✓Drug-related TEAE: effets indésirables survenant au cours de traitement et liés au traitement (évaluation de l'investigateur)

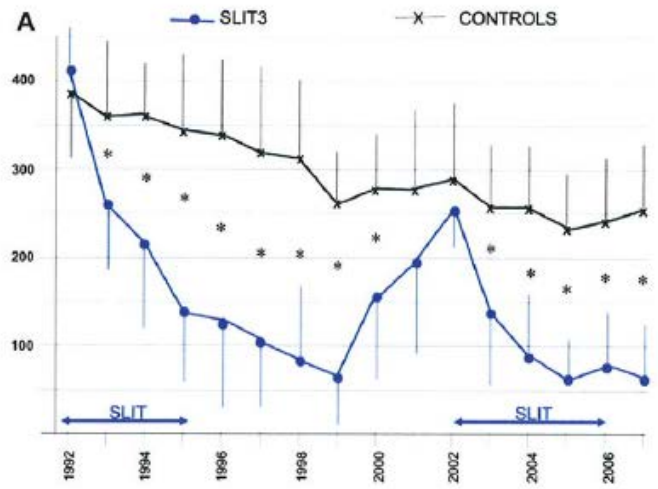
Conclusions

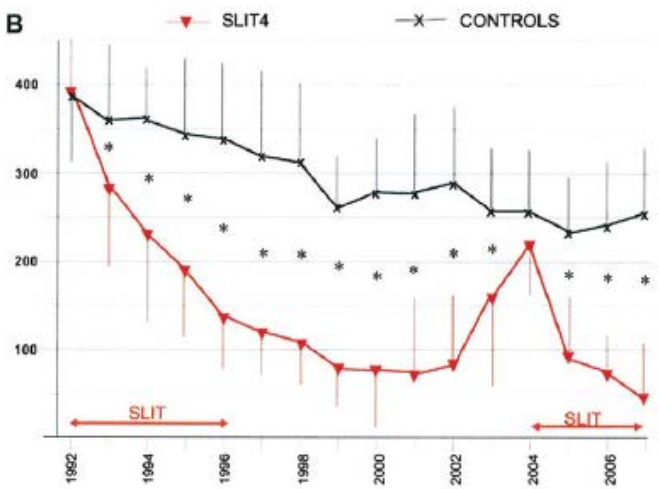
✓Effet dose-réponse clair de 100IR à 500IR

✓Le groupe 500IR présente la plus grande réduction du score de symptômes

✓Tolérance comparable de toutes les doses testées

Effet long-terme ITA/SLIT Acariens MS, 15 ans, 59 A/12 C

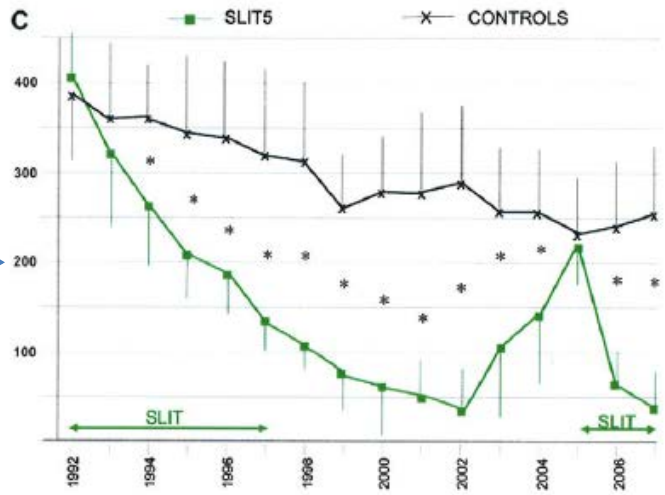




D3: 7ans OK

D4: 8-10 ans OK

Persistance de l'effet si le SMS score < 50% de la valeur au baseline



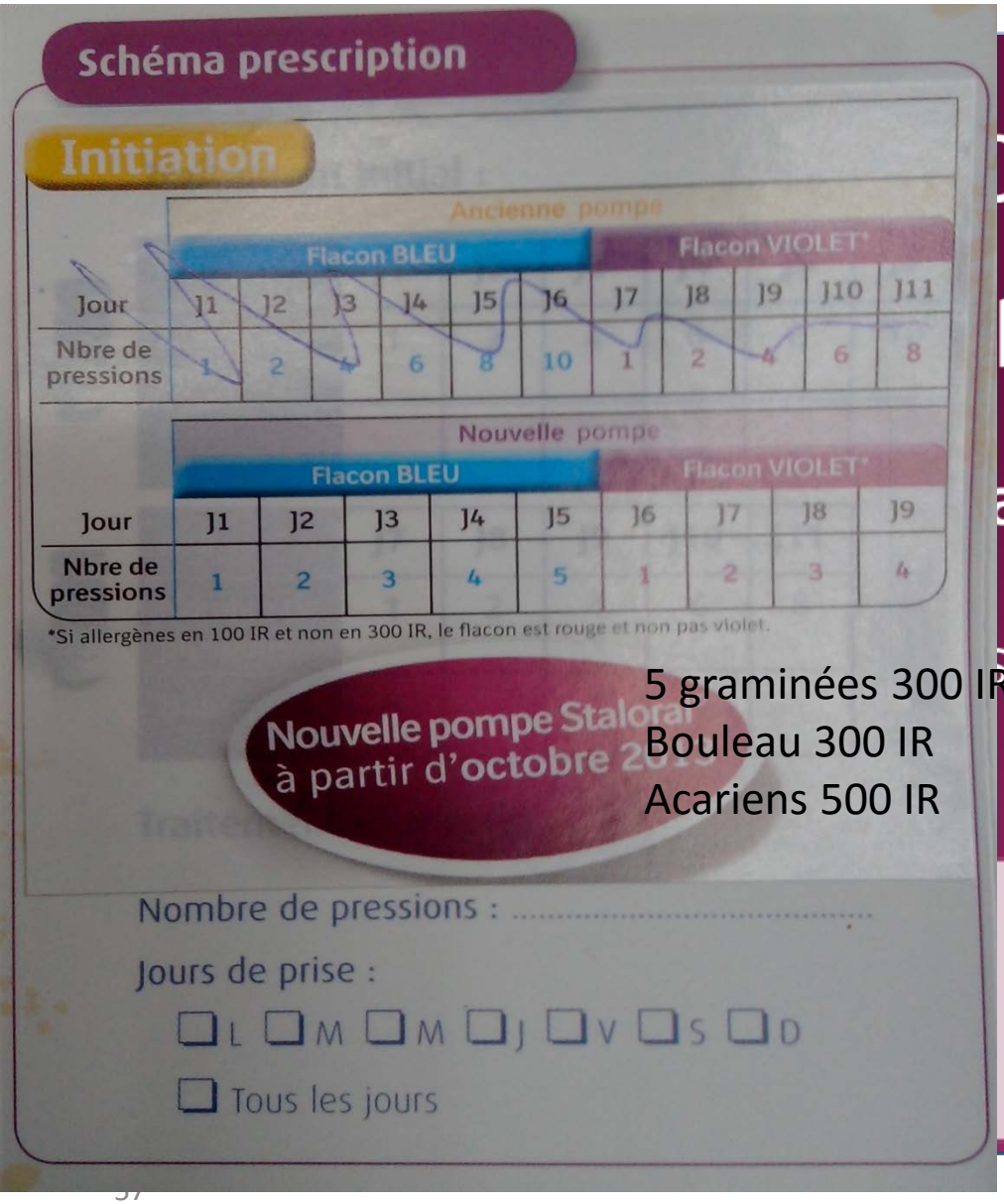
D5: 8-10 ans OK

FIG 2. Mean monthly SMSs (means and SDs) throughout the 15 years of the study in patients in the SLIT3 **(A)**, SLIT4 **(B)**, and SLIT5 **(C)** groups. The duration of SLIT treatment is indicated by *arrows* at the bottom. The *asterisks* indicate a significant difference versus the control group.

Marogna et al J. Allergy Clin. Immunol. 2010; 126 (5): 969 - 975

Nouvelle pompe Staloral : trend de majoration des doses

Nouvelle pompe Staloral : trend de majoration des doses



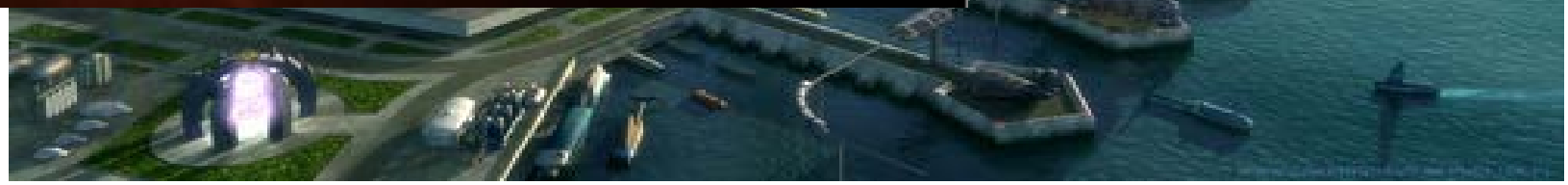
5 graminées 300 IR 4/5p
Bouleau 300 IR 4/5p
Acariens 500 IR ?7/8p

EBM …mais comment en pratique.

- Quel allergène ?
- Doses ?
- SCIT/SLIT: solution, comprimé ?
- Pré/ Co saisonnier ?
- Combien de temps ?
- Quels bénéfices en pratique ?
- Pour qui ?
- Efficace après combien de mois ?
- Pour quelle durée ?
- Pour quel allergènes ?

- New well-powered, well-designed studies using standardised products will provide robust and definitive information regarding optimal dose, regimen, duration and post-treatment effect of house

Avenir de l'ITA …



Marqueurs de l'efficacité de l'ITA ?

- Efficacité clinique **a posteriori**
  - Scores cliniques a postériori
- Diminution des la consommation des médicaments
  - Scores de consommation médicamenteuse
- Non confirmés
  - IGE/RAST: ----
  - TCA :---
  - IGG4 ou IGG1 anti AG spécifiques : --
  - IGA2: ---

Clin Exp Allergy. 1993 Aug;23(8):647-60.

Venom-specific IgG antibodies in bee and wasp allergy: lack of correlation with protection from stings.

Ewan PW, Deighton J, Wilson AB, Lachmann PJ.

Molecular Immunopathology Unit, MRC Centre, Cambridge, U.K.

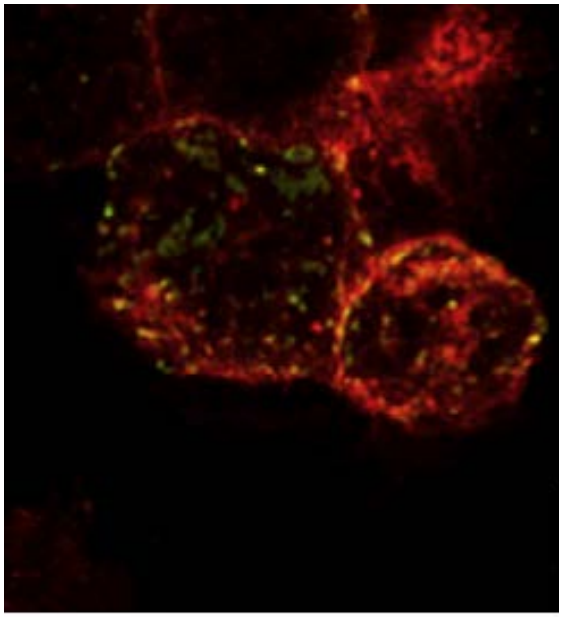
1993 **+-20 ans** **2011/2012/2013**

Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies

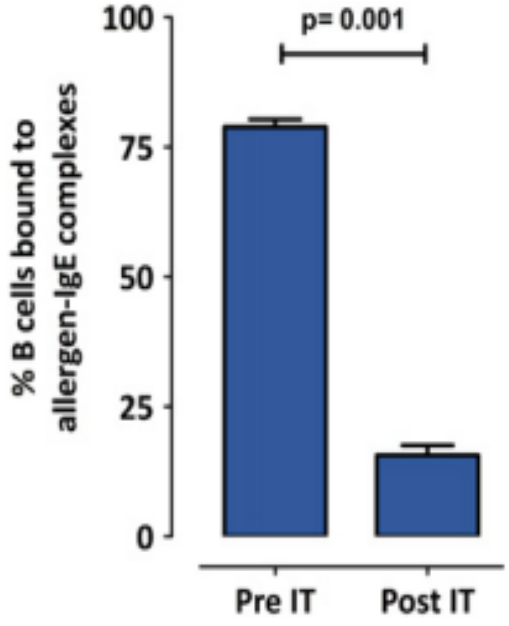
13 SCIT (7: 2+2 ans; 6: 2 ans puis placebo)

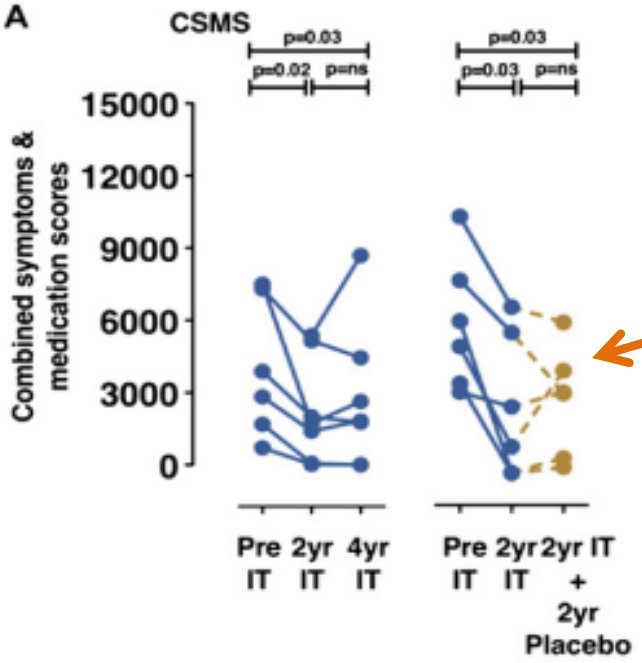
Louisa K. James, PhD,[a]* Mohamed H. Shamji, PhD,[a]* Samantha M. Walker, PhD, RGN,[a] Duncan R. Wilson, MD, FRCP,[a] Petra A. Wachholz, PhD,[a] James N. Francis, PhD,[a] Mikila R. Jacobson, PhD,[a] Ian Kimber, PhD,[b] Stephen J. Till, PhD, MRCP,[a] and Stephen R. Durham, MD, FRCP[a] *London and Manchester, United Kingdom*

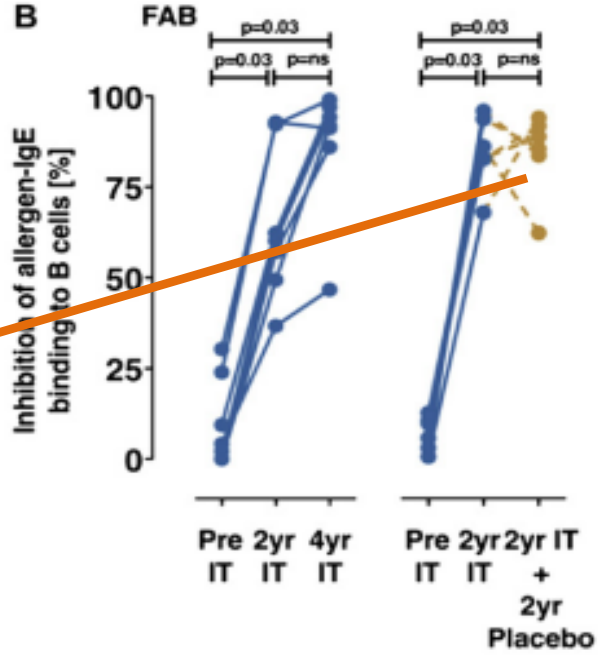
Conclusion: Grass pollen immunotherapy induces a subpopulation of allergen-specific IgG antibodies with potent inhibitory activity against IgE that persists after treatment discontinuation and that could account for long-term clinical tolerance. (J Allergy Clin Immunol 2011;127:509-16.)

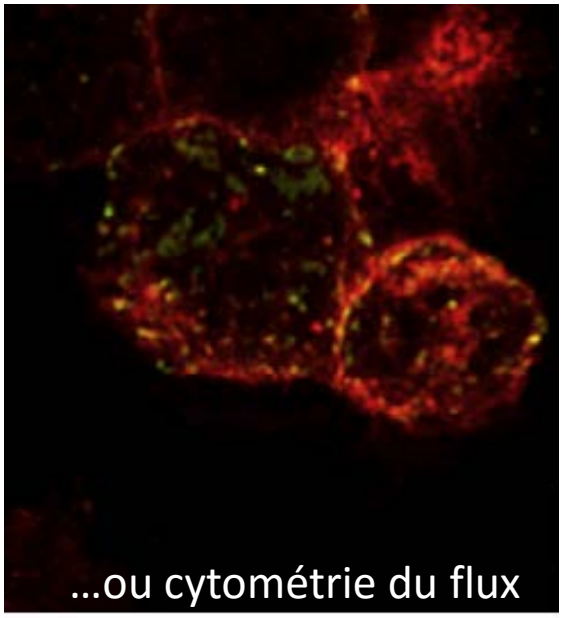


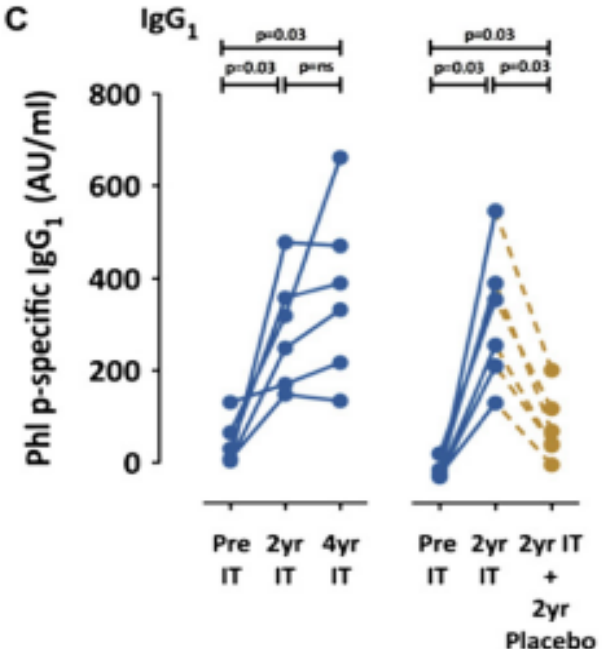
Visualization of CD23 receptor coaggregation and allergen-IgE complexes binding to B cells

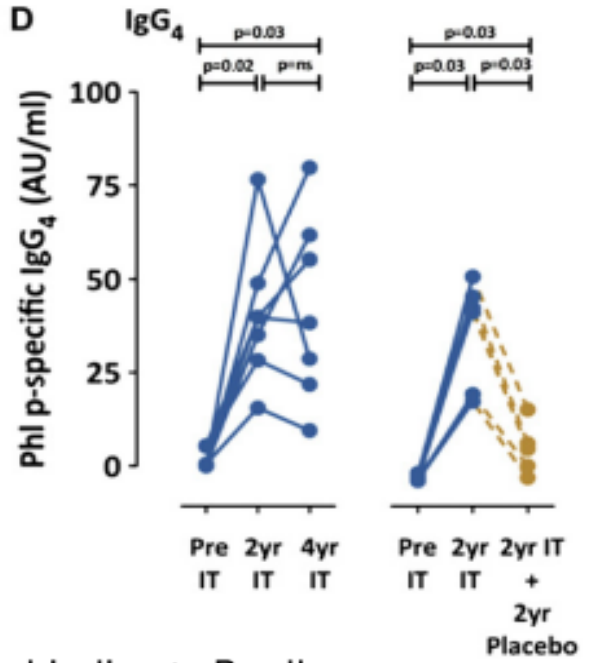












Visualization of CD23 receptor coaggregation and allergen-IgE complexes binding to B cells

Long-term tolerance after allergen immunotherapy is accompanied by selective persistence of blocking antibodies

Louisa K. James, PhD,[a]* Mohamed H. Shamji, PhD,[a]* Samantha M. Walker, PhD, RGN,[a] Duncan R. Wilson, MD, FRCP,[a] Petra A. Wachholz, PhD,[a] James N. Francis, PhD,[a] Mikila R. Jacobson, PhD,[a] Ian Kimber, PhD,[b] Stephen J. Till, PhD, MRCP,[a] and Stephen R. Durham, MD, FRCP[a] *London and Manchester, United Kingdom*

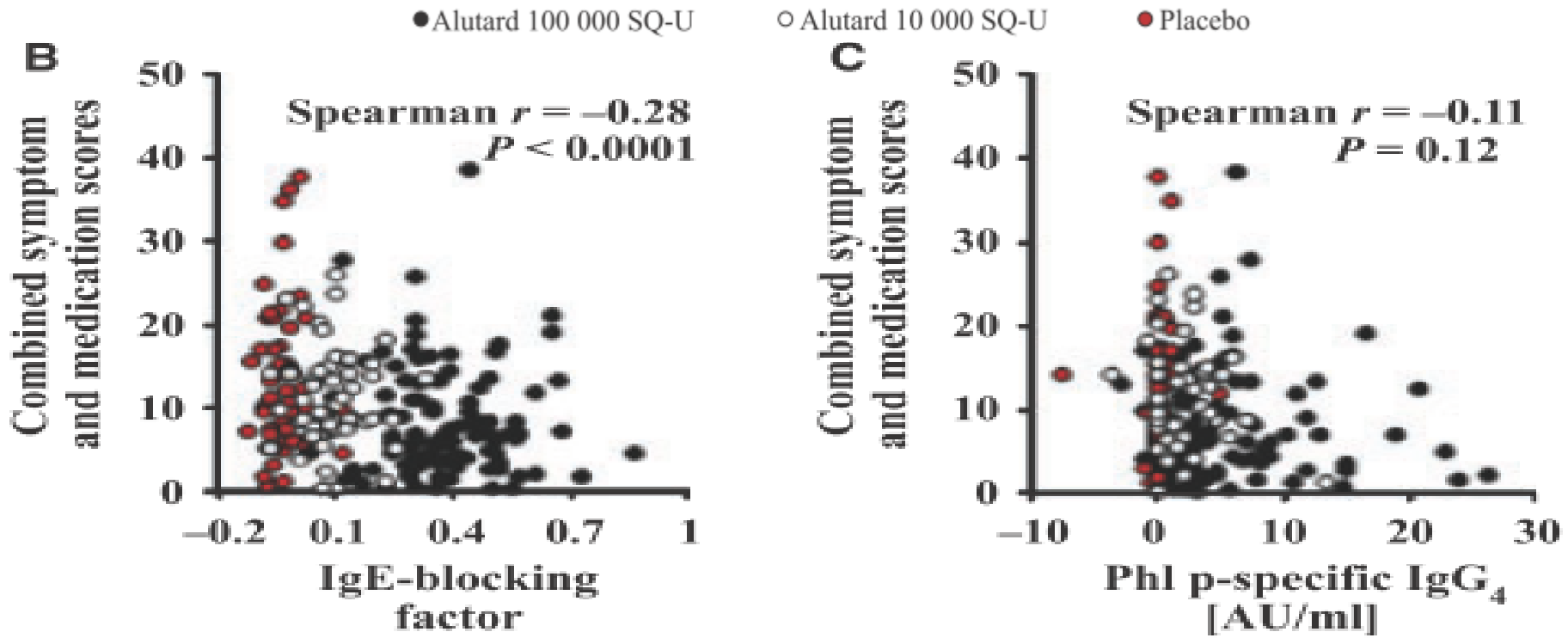
Results: Clinical improvement was maintained after 2 years of discontinuation. Although immunotherapy-induced grass pollen–specific IgG1 and IgG4 levels decreased to near-preimmunotherapy levels during discontinuation, inhibitory bioactivity of allergen-specific IgG antibodies was maintained unchanged.

Conclusion: Grass pollen immunotherapy induces a subpopulation of allergen-specific IgG antibodies with potent inhibitory activity against IgE that persists after treatment discontinuation and that could account for long-term clinical tolerance. (J Allergy Clin Immunol 2011;127:509-16.)

Functional rather than immunoreactive levels of IgG_4 correlate closely with clinical response to grass pollen immunotherapy

Allergy 2012 ; 221 SCIT Phleum Pratense 8 mois

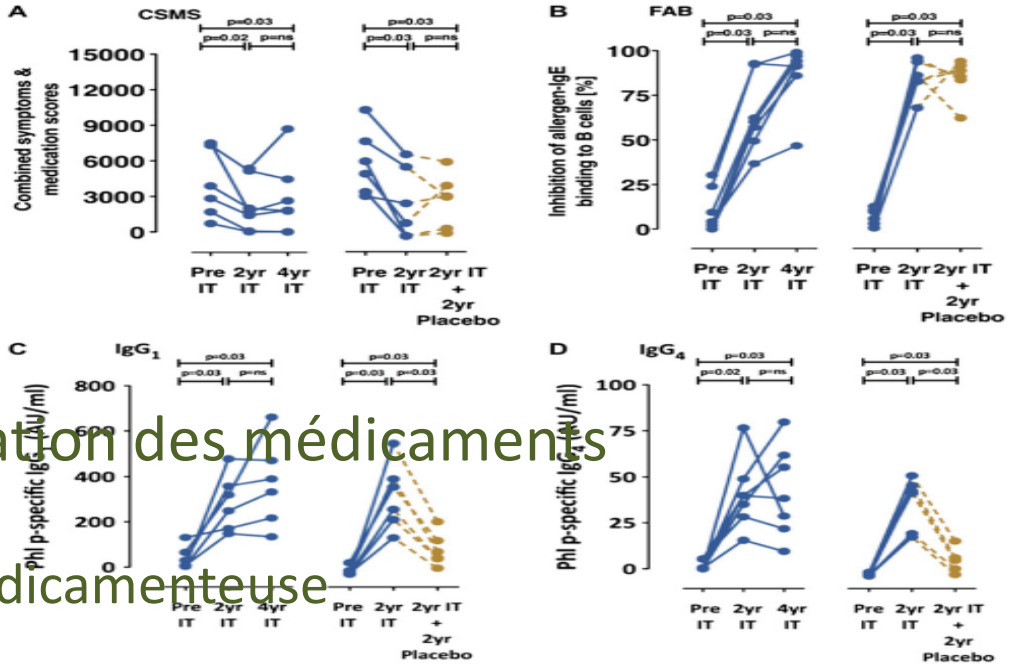
M. H. Shamji[1], C. Ljørring[2], J. N. Francis[1], M. A. Calderon[1], M. Larché[3], I. Kimber[4], A. J. Frew[5], H. Ipsen[2], K. Lund[2], P. A. Würtzen[2] & S. R. Durham[1]



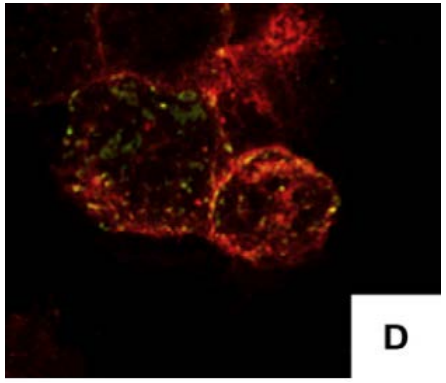
Conclusions: Functional assays of inhibitory IgG_4 and IgE-blocking factor may be more useful surrogates of clinical response than IgG_4. Whether these antibody effects may serve as predictive biomarkers of clinical efficacy in individual patients requires further investigation.

Marqueurs de l'efficacité de l'ITA ?

- Efficacité clinique
  - **a posteriori**
  - Scores cliniques
- Diminution des la consommation des médicaments
  - **a posteriori**
  - Scores de consommation médicamenteuse



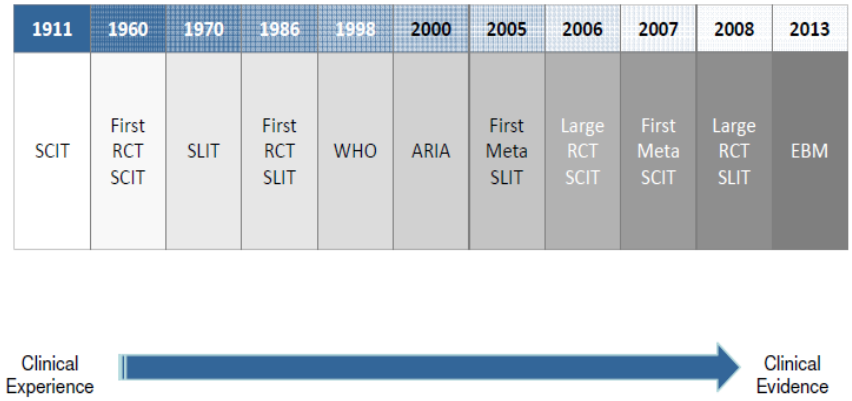
- **Intérêts des marqueur biologique de l'efficacité e l'ITA ?**
  - **Compréhension de l'effet thérapeutique**
  - **Détecter tôt répondeurs et non répondeurs**
  - **Adaptation de la dose: individualisation ?**
  - **Adaptation de la durée du traitement**
  - **Suivi , prévoir quand redémarrer l'ITA**
    - **Analyses a priori**



Conclusions/ Take-home messages

- En questions/ Quiz

???



...cet après-midi

Merci de votre attention.