

# New Medical Treatments for Nasal Polyps

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## Disclosures

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app

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42nd Annual Pulmonary and Allergy Update

## Objectives

1. Discuss the epidemiology, biology, pathophysiology, and symptoms of CRS with nasal polyposis (CRSwNP).
2. Review treatment guidelines and recommendations for CRSwNP.
3. Review the many scoring systems used to evaluate CRSwNP.
4. Discuss in detail the Phase II and Phase III clinical trials using biologics for treatment of CRSwNP.

# Nasal Polyposis Epidemiology

Prevalence = ~4%<sup>1</sup>; (CRS = ~11-12%)<sup>2</sup>  
 Increases with age; peak ~50 years  
 Male to female = 2:1  
 Association with allergic rhinitis is weak.

Genetic inheritance = ~14%  
 Caucasians = Th2-driven inflammation.  
 Asians = Th1-driven inflammation.

**Costs:**  
 CRS = ~\$8 billion/year<sup>2</sup>  
 Per patient per year: \$13,000;  
 \$26,000 if surgery performed.  
 Surgeries/year = ~500,000

Disease	Prevalence estimates
Allergic rhinitis	Adult: 0.1%; Children 1.5% <sup>1</sup>
Asthma	5-22%
CRS	20-25% <sup>1-4</sup>
NSAID intolerance	36-72%
NSAID intolerance and asthma	80%
Allergic fungal sinusitis	80%
Eosinophilic granulomatosis with polyangiitis (EGPA)	50%
Cystic fibrosis	Adult 40%; Children 10%
Primary ciliary dyskinesia	40%
Inflammatory bowel disease	17.5%
Atopic dermatitis	16.5%

1. Hastan, Fokkens, et al, 2011
2. Lange, Holst, et al., Clin Otolaryngol 2013.
3. Mygind. JACI. 1990 Dec;86(6 Pt 1):827-9.
4. Schleimer RP. Annu Rev Pathol. 2017;12:331-57.
5. Hunter TD, DeConde AS, Manes RP. J Med Econ. 2018;21(6):610-5.
6. Palmer JN, Messina JC, Bilech R, et al. Allergy Asthma Proc. 2018;39:1-9.
7. Pearlman AN, Chandra RK, Chang D, et al. Am J Rhinol Allergy. 2009;23(2):145-8.
8. Tomassen, Vandeplas et al, JACI, 2016

# Definition: European Position Paper on Rhinosinusitis and Nasal Polyps

Rhinosinusitis in adults	Rhinosinusitis in children
<p><b>Definition:</b></p> <ul style="list-style-type: none"> <li>inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):               <ul style="list-style-type: none"> <li>± facial pain/pressure</li> <li>± reduction or loss of smell</li> </ul> </li> <li>and either               <ul style="list-style-type: none"> <li>endoscopic signs of                   <ul style="list-style-type: none"> <li>nasal polyps, a</li> <li>mucopurulent discharge from the middle meatus and/or maxillary sinus</li> <li>edema/mucosal thickening of the middle meatus</li> </ul> </li> </ul> </li> <li>and/or               <ul style="list-style-type: none"> <li>CT changes:                   <ul style="list-style-type: none"> <li>mucosal changes within the ostiomeatal complex and/or sinuses</li> </ul> </li> </ul> </li> </ul>	<p><b>Definition:</b></p> <ul style="list-style-type: none"> <li>inflammation of the nose and the paranasal sinuses characterized by two or more symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip):               <ul style="list-style-type: none"> <li>± facial pain/pressure</li> <li>± reduction or loss of smell</li> </ul> </li> <li>and either               <ul style="list-style-type: none"> <li>endoscopic signs of                   <ul style="list-style-type: none"> <li>nasal polyps, a</li> <li>mucopurulent discharge from the middle meatus and/or maxillary sinus</li> <li>edema/mucosal thickening of the middle meatus</li> </ul> </li> </ul> </li> <li>and/or               <ul style="list-style-type: none"> <li>CT changes:                   <ul style="list-style-type: none"> <li>mucosal changes within the ostiomeatal complex and/or sinuses</li> </ul> </li> </ul> </li> </ul>

**Summary definition:** inflammation of nasal cavity and paranasal sinuses characterized by 12 weeks of persistent symptoms that include (1) congestion, (2) discharge, (3) pain or facial pressure, (4) impairment in sense of smell, and (5) fatigue.

## Question: Which of the following is false?

1. With a peak at ~50 years of age, nasal polyps are more common in males than females.
2. Caucasians are more likely to have Type-1 inflammatory as a driver for nasal polyps than Asians.
3. Greater than 80% of patients with asthma and NSAID allergy have nasal polyps.
4. Allergic rhinitis is strongly associated with CRSwNP.
5. CRS is defined as inflammation of nasal cavity and paranasal sinuses characterized by 12 weeks of persistent symptoms that include (1) congestion, (2) discharge, (3) pain or facial pressure, (4) impairment in sense of smell, and (5) fatigue.

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# Definition: Acute vs. Chronic; Severity (EPOS)

## Acute

- (1) < 12 weeks
- (2) Complete resolution of symptoms

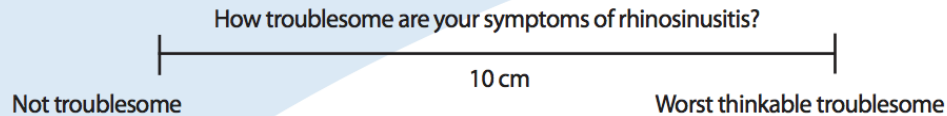
## Chronic

- (1) ≥ 12 weeks
- (2) Without complete resolution of symptoms (may be subject to exacerbations)

Visual Analog Scale (VAS): Rating system from 0 (none) to 10 (most severe)

Radiographic findings in CRSwNP

To evaluate the total severity, the patient is asked to indicate on a VAS the answer to the question:



MILD = VAS 0-3  
MODERATE = VAS >3-7  
SEVERE = VAS >7-10



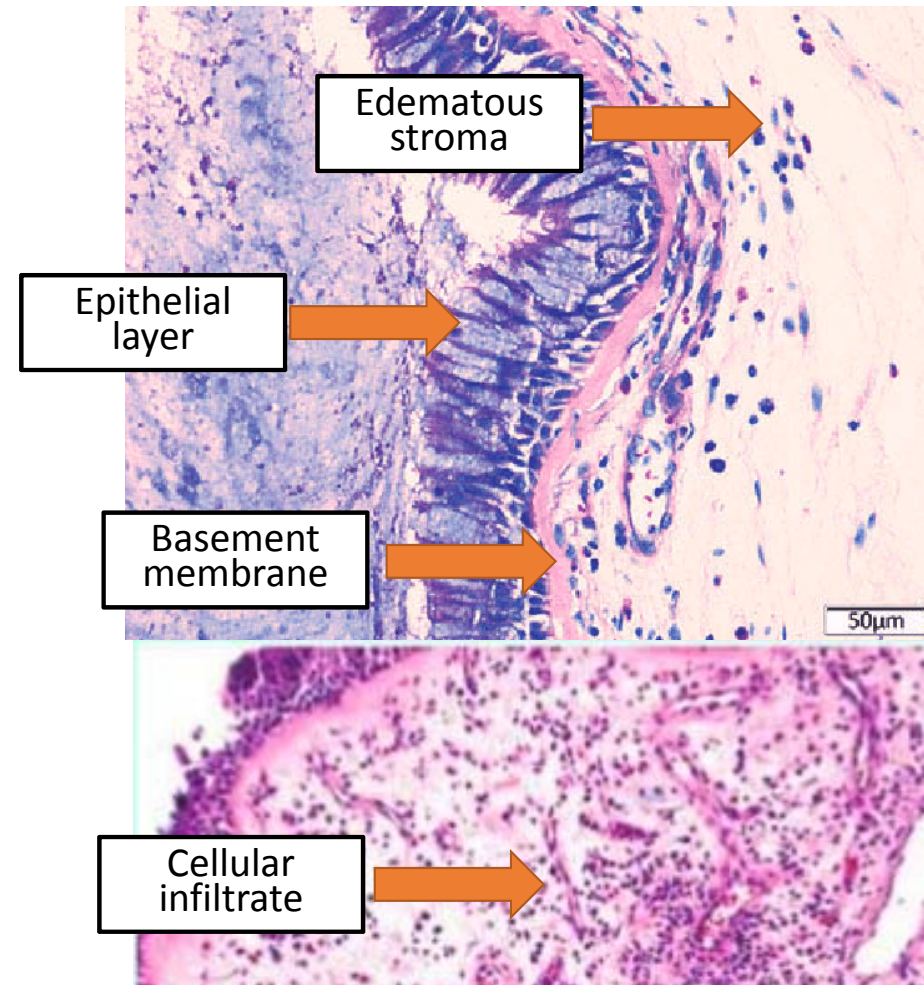
Control

Severe CRSwNP



# Histology of polyps

1. Described as a ‘fluid filled sack’ originating in the sinuses
2. Edematous and fibrotic stroma
3. Thickened basement membrane
4. Thickened epithelial layer
5. Eosinophils (> 60%); particularly prevalent between epithelial cell layer and thickened basement membrane.
6. Increased #'s of degranulated mast cells
7. Lymphocytes
8. B-cells/lymphoid tissue



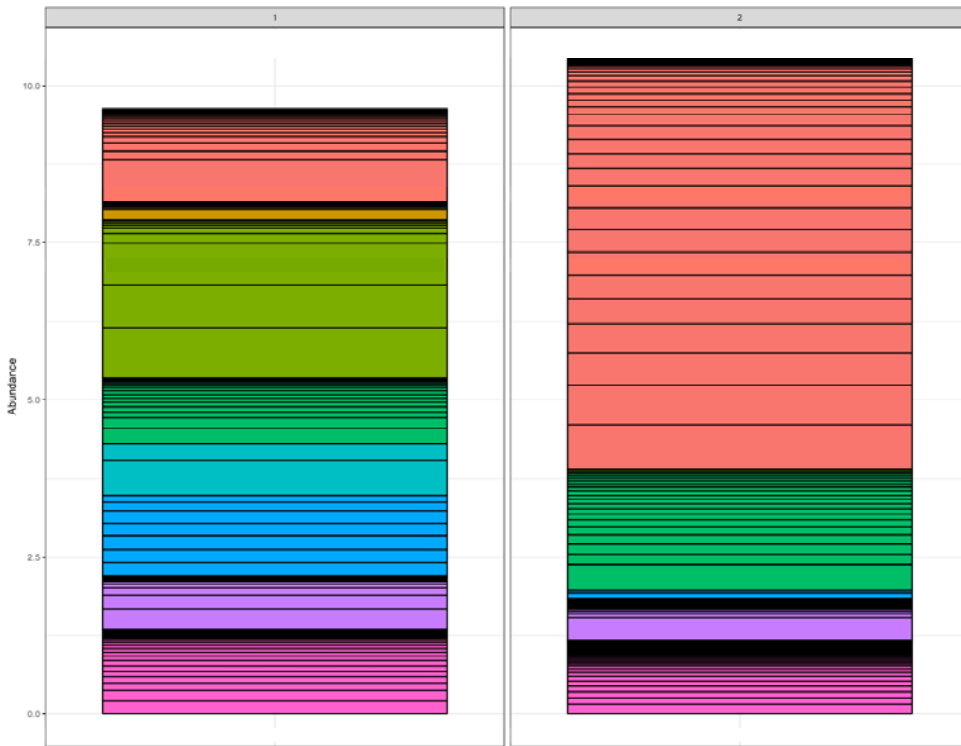
## Mechanisms of Inflammation in Nasal Polyps

Effectors	Evidence	Likely role(s)
Th2 cells	(1) Elevated IL-4, IL-13 in nasal lavage (2) Success of dupilumab (anti-IL4Ra/IL13Ra antibody)	IL-4, IL-5, and IL-13, secreted by Th2 cells and ILC2 cells, are the <b>major drivers of NP formation</b> . <sup>1-2</sup>
Eosinophils	(1) 60% of NPs (2) IL-5 & eotaxin in nasal lavage	(1) Accumulation of eosinophils via IL-5 is likely first step in polyp formation
Mast cells	(1) Degranulation (2) Tryptase in nasal fluid	
B cells	(1) Lymphoid tissue in NPs (2) IgE to staphylococcal enterotoxins within NPs (3) Elevated total IgE in patients NPs	(1) IgE production contributes to inflammation.
Epithelial cells	(1) Thickened, increased mucous-producing cells	Activated epithelial cells contribute to persistent underlying inflammation.

**Summary definition of polyps:** Sacs consisting of a thick basement membrane holding fluid and eosinophilic-rich inflammatory cells that have grown from the sinuses into the middle meatus.

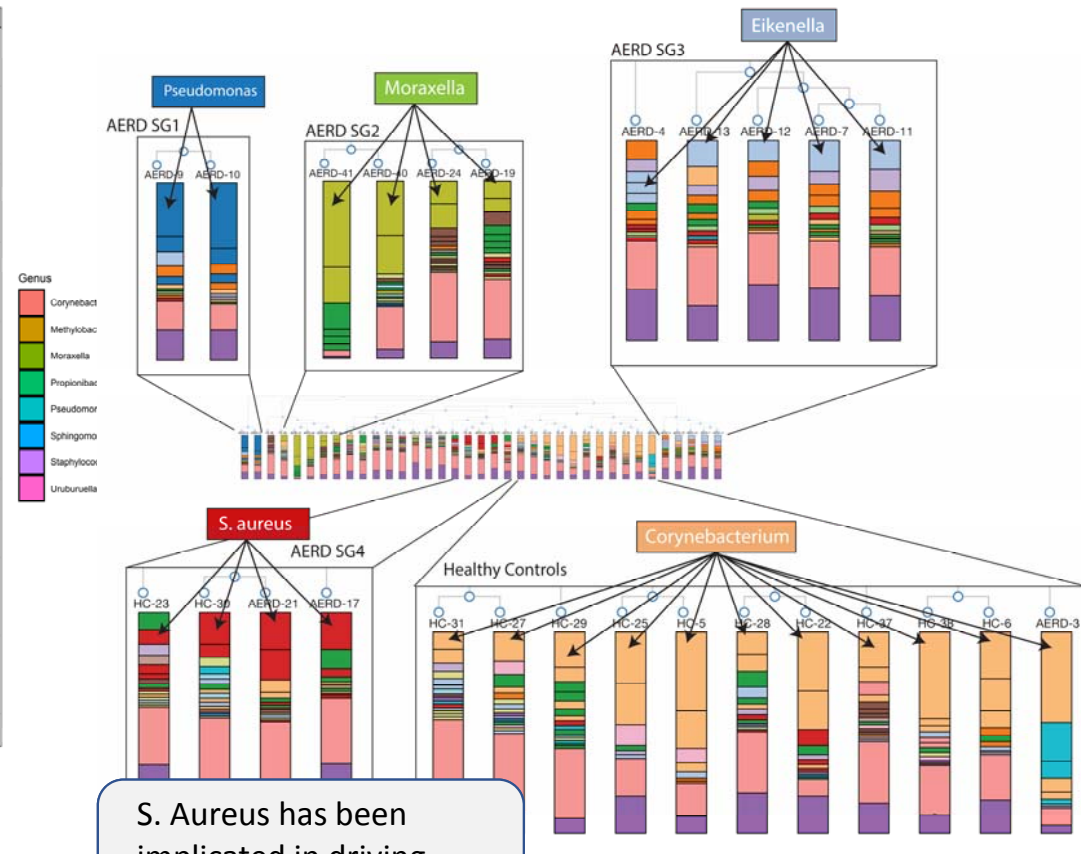
1. Khan A, Vandeplass G, Huynh TMT, et al. Rhinology. 2019;57(1):32-42.  
2. Peters AT, Spector S, Hsu J, et al. Ann Allergy Asthma Immunol. 2014;113(4):347-85.

# Microbiome alteration in patients with CRSwNPs.



AERD: many pathogenic bacterial species

Controls: mostly Corynebacterium, i.e. normal flora



S. Aureus has been implicated in driving inflammation.

## Question: Which of the following is false?

1. Polyps can be described as 'fluid filled sacs.'
2. Polyps are characterized by a thickened basement membrane surrounding edematous and fibrotic stroma.
3. Eosinophils can make up over 60% of nasal polyps.
4. There are increased numbers of degranulated mast cells present.
5. Polyps typically originate in nasal cavity outside of the sinuses.

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# Affect of CRSwNP on Quality of Life is Significant and Underappreciated.

Early symptoms	Late symptoms
Rhinorrhea Sneezing	Congestion (93.5% most common) Waking up tired (69.9%; 3 <sup>rd</sup> most common) Loss of sense of smell/taste Pain or facial pressure Fatigue

## Quality of life issues\*

- Symptoms often last for many years
- Socially unacceptable nasality of the voice
- Loss of sense of smell and taste
- **Fatigue**
- Lack of sleep
- Feelings of being 'unwell,' affecting confidence and self-identity.
- Using the SF-36, NPs significantly reduced QoL across 7/8 domains, including bodily pain, general health, vitality, role emotional, social functioning, mental health, and role physical<sup>1</sup>
- Leads to workplace absenteeism<sup>2</sup>
- 15% of patients have 4-6 procedures in 8 years<sup>3</sup>

\* Note: tools to define disease severity *are not well defined* at this point.

1. Alobid, Benitez, et al. Allergy 2005.
2. Sahlstrand-Johnson P, et al, Rhinology 2011
3. Bhattacharyya N, et al, Otolaryngol Head Neck Surg 2011

# Treatment Evidence and Recommendations for CRS WITHOUT Nasal Polyps

Therapy	Level	Grade of recommendation	Relevance
steroid – topical	Ia	A	yes
nasal saline irrigation	Ia	A	yes
bacterial lysates (OM-85 BV)	Ib	A	unclear
oral antibiotic therapy short term < 4 weeks	II	B	during exacerbations
oral antibiotic therapy long term ≥12 weeks**	Ib	C	yes, especially if IgE is not elevated
steroid – oral	IV	C	unclear
mucolytics	III	C	no
proton pump inhibitors	III	D	no
decongestant oral / topical	no data on single use	D	no

Therapy	Level	Grade of recommendation	Relevance
allergen avoidance in allergic patients	IV	D	yes
oral antihistamine added in allergic patients	no data	D	no
herbal medicine	no data	D	no
immunotherapy	no data	D	no
probiotics	Ib (-)	A(-)	no
antimycotics – topical	Ib (-)	A(-)	no
antimycotics - systemic	no data	A(-)	no
antibiotics – topical	Ib (-)	A(-) <sup>§</sup>	no

\* Some of these studies also included patients with CRS with nasal polyps

° Acute exacerbations of CRS should be treated like acute rhinosinusitis

# Ib (-): Ib study with a negative outcome

§ A(-): grade A recommendation **not** to use

\*\* Level of evidence for macrolides in all patients with CRSsNP is Ib, and strength of recommendation C, because the two double blind placebo controlled studies are contradictory; indication exists for better efficacy in CRSsNP patients with normal IgE so the recommendation is A. No RCTs exist for other antibiotics

# Treatment Evidence and Recommendations for CRS WITH Nasal Polyps

Therapy	Level	C <sup>o</sup>	yes, small effect	mucolytics	no data	D	no
topical steroids	Ia	<b>Summary:</b> Mainstay of treatment are intranasal steroids, short courses of steroids, antibiotics and saline rinses; but only steroids are given a Grade A recommendation.					
oral steroids	Ia						
oral antibiotics short term <4 weeks	1b and 1b(-)	<b>Summary:</b> In general, less likely to respond to antibiotics and more likely to respond to corticosteroids.					
oral antibiotic long term ≥ 12 weeks	III						
capsaicin	II	<b>Summary:</b> Good evidence to support aspirin desensitization if +AERD.					
proton pump inhibitors	II						
aspirin desensitisation	II						
furosemide	III	<b>Summary:</b> ~1/3 are not controlled with current standard of care approach.					
immunosuppressants	IV						
nasal saline irrigation	Ib, no data in single						
topical antibiotics	no data						
anti-IL5	no data	Recommendation C.					



## Question: Which of the following is false?

1. ~1/3 of patients with CRSwNP are not controlled with current standard of care approach.
2. It is recommended to give oral steroids must courses of 3 weeks or more.
3. CRSwNP subjects are less likely to respond to antibiotics and more likely to respond to corticosteroids.
4. Short courses of oral steroids are Grade A recommendation.

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4. Short courses of oral steroids are Grade A recommendation.

# Steroids for treatment of CRSwNP

Topical Nasal Steroids	Systemic Steroids
<ul style="list-style-type: none"><li>• Nasal steroid spray reduces rhinitis symptoms and polyp size, delays the recurrence of polyps after polypectomy.<ul style="list-style-type: none"><li>❖ Note: nasal steroids have limited effect on the size of nasal polyps.</li></ul></li><li>• Typically more effective in mild disease</li><li>• Required after nasal surgery</li><li>❖ <b>Grade A Recommendation</b></li></ul>	<ul style="list-style-type: none"><li>• Short-term use of oral steroids (1-3 weeks) reduces polyp size and improves symptoms, although improvements are typically temporarily.</li><li>• Associated with increased risks of gastrointestinal disturbance, insomnia and long-term risks of obesity, loss of bone mineralization, diabetes, hypertension, heart disease.<ul style="list-style-type: none"><li>❖ Note: Even repetitive short-term use of systemic corticosteroids is associated with significant health risks.</li></ul></li><li>• Recommended typically at short courses (5-10 days) for severe nasal obstruction and always in combination with topical nasal steroids.</li><li>❖ <b>Grade A Recommendation</b></li></ul>

# Nasal Surgery

Nasal surgery ranges from simply polypectomy to full removal of polypoid mucosal tissue from sinuses.

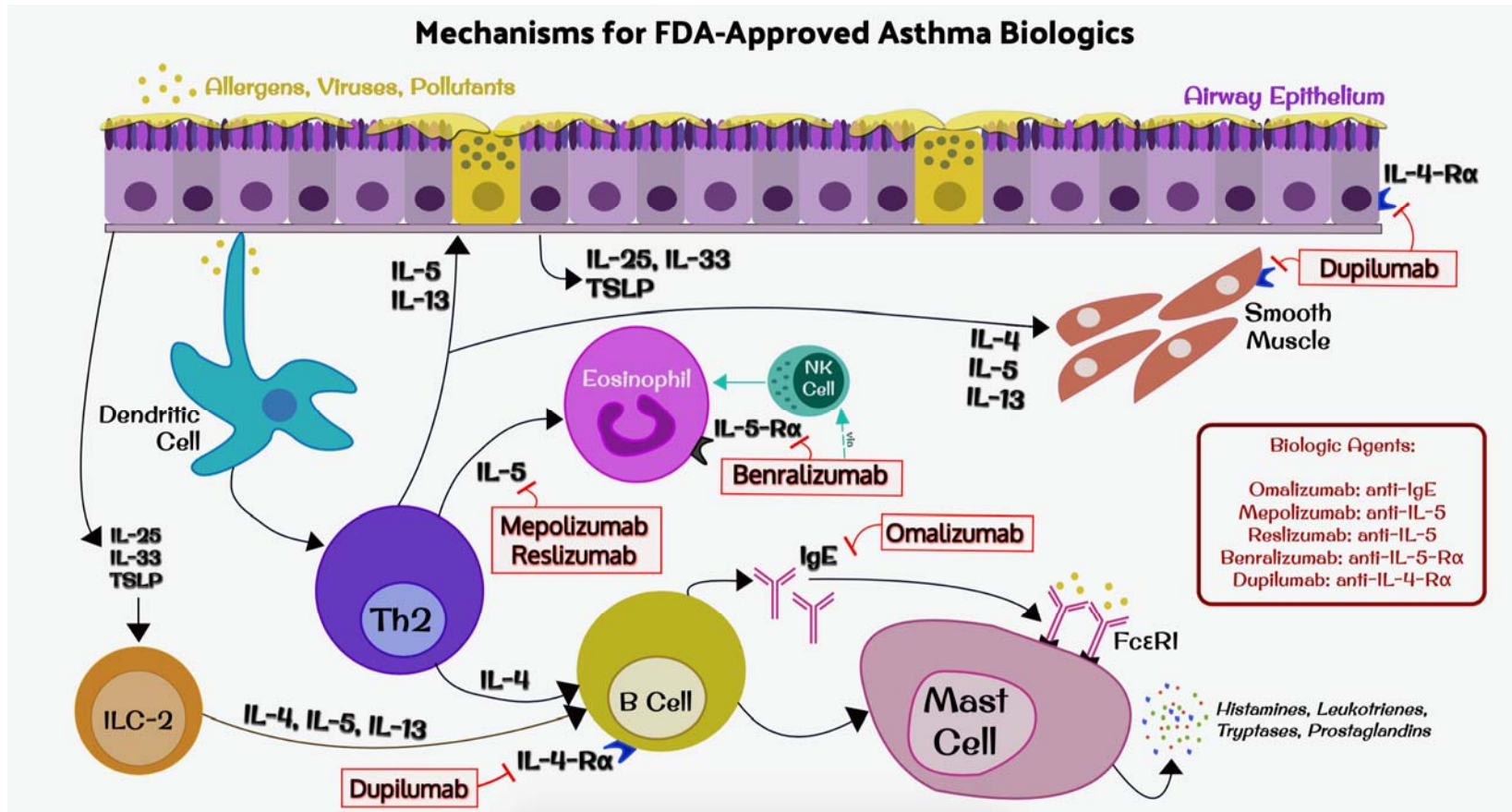
- ~500,000 CRS surgeries per year<sup>1-2</sup>
- ~90,000 uncontrolled despite recent oral corticosteroids or surgery
- 59% → undergo revision surgery
- 30% → multiple surgeries, sometimes up to 15-20X's\*
- 23% → 4 or more revision surgeries (GALEN Study)
- 40% → recurrent
- 80% → inadequate

**Summary:** New and better therapies are needed to spare patients from repeated sinus surgeries and systemic steroids.

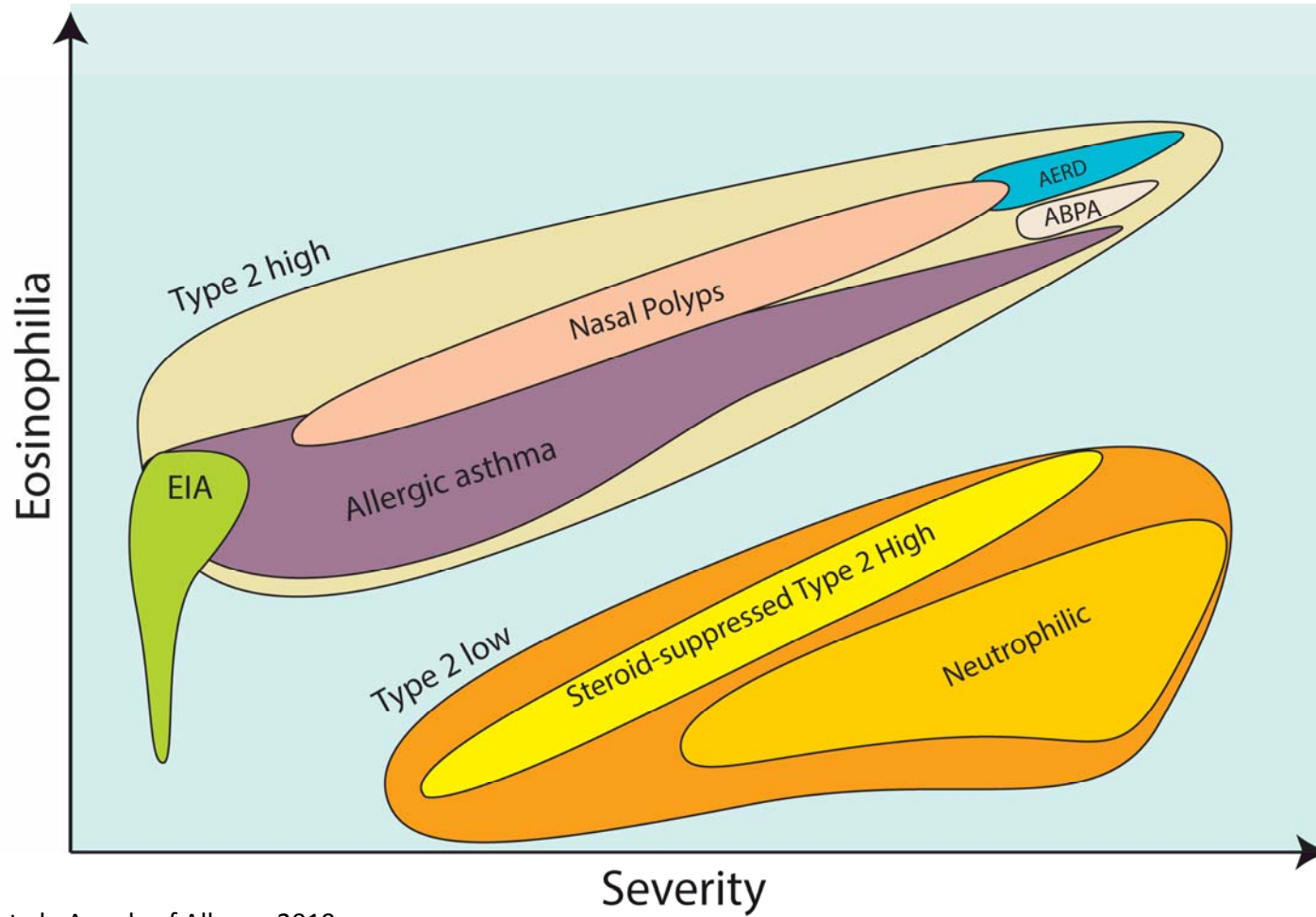
\*Subsequent surgeries tend to take longer and be more difficult.

1. Bhattacharyya, Orlandi et al, 2011
2. Schleimer, Robert. Annual Rev Pathol. 2017
3. DeConde, Mace et al, The Laryngoscope, 2017.

# Mechanism of Action of the 5 Asthma Biologic Therapies



# Phenotypes of Asthma



# Many Scoring Systems and Measures of Efficacy

❖ Note: Correlation of endoscopy scoring systems and disease-specific quality of life (QoL) measures have found no or (at best) weak correlations.<sup>1</sup>

Score	Type	Description
Total nasal endoscopic polyp score (TPS)	Endoscopic scoring system	Ranges 0-8. 0 = no polyps, 1 = polyps confined to the middle meatus, 2 = multiple polyps occupying the middle meatus, 3 = polyps extending beyond middle meatus, 4 = polyps completely obstructing the nasal cavity. Both sides added.
Lund-Mackay	CT score	Ranges 0-24. The paranasal sinuses and ostiomeatal complex are assigned a score of 0 (no abnormality), 1 (partial opacification) and 2 (complete opacification).
UPSIT	Symptom/QoL score	Ranges 0-40, measures olfactory improvement; higher scores 35-40 = normal sense of smell
VAS	Symptom/QoL score	0-10 cm, asks 'how troublesome are your symptoms of rhinosinusitis?'
SNOT-22	Symptom/QoL score	Validated, CRS-specific outcome measure consisting of 22 items
SF-36	QoL score	Non-CRS specific measure of health status that assesses physical functioning, physical role, bodily pain, general health, vitality, social functioning, emotional role functioning and mental health.
RSOM-31	Symptom/QoL score	Validated, CRS-specific outcome measure consisting of 31 items and grouped into 7 domains: nasal, eye, sleep, ear, general symptoms, practical problems and emotional.
AQLQ	QoL score	Asthma-specific, health-related quality of life instrument including 32 items assessing both physical and emotional impact of disease.
ACQ5	Symptom/QoL score	Validated, simple questionnaire to measure the adequacy of asthma control.
Nasal airflow (PnIF)	Physiological measurement	Inexpensive, rapid, objective measure of the nasal airflow during maximal inspiration.
Sniffin' Sticks Screening	Smell test	12 different odors presented and asked to identify a source from a list of 4 options.

MOU2

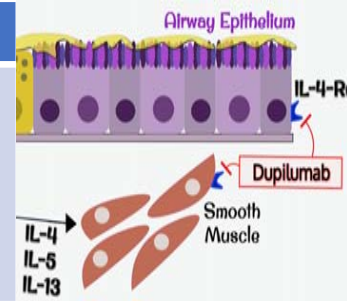
1. Deconde A. International forum of allergy & rhinology. 2016.





# Dupilumab: FDA-Approved for Treatment of Nasal Polyposis.

Mechanism	What it means?	FDA Approval
Type 2 cytokines, IL-4 and IL-13 drive many of the small airway and mucosal changes associated with asthma. Binds the IL-4 receptor $\alpha$ chain (IL-4R $\alpha$ ), blocking both IL-4 and IL-13 receptors and their signaling	Effectively and directly blocks Type 2 inflammatory signaling	(1) Atopic dermatitis (12 years and older) (300mg dose) (2) Asthma (12 years and older) with an eosinophilic phenotype (150mg or 300mg dose) or with oral corticosteroid dependent (300mg dose) (3) Adults with CRSwNP



**Phase II Trial;** DBRCT; 60 total patients; Dose = 600mg loading, 300mg weekly doses x 15

(Bachert et al., *Effect of Subcutaneous Dupilumab on Nasal Polyp Burden in Patients With Chronic Sinusitis and Nasal Polyposis*, JAMA, 2016)

**Structure:** 4-week run-in; 16 weeks of treatment, 16 weeks of follow up;

❖ Treatment with mometasone furoate 100 mg each nostril twice daily during run-in and through-out

**Inclusion criteria:** Ages 18-65, bilateral nasal polyposis refractory to steroids (at least 2 months of intranasal steroids)

❖ Required:

(1) **total endoscopic nasal polyp** score  $\geq 5$  and a minimal 2 in each nostril

(2)  $\geq 2$  of the following symptoms: nasal obstruction or discharge, facial pain or pressure, reduction or loss of sense of smell

**Exclusion criteria:** (1) Received steroids, monoclonal antibodies, immunosuppressive treatment in last 2 months, OR (2) any nasal surgery in last 6 months or  $> 2$  NP surgeries total, OR previously part of a dupilumab trial.

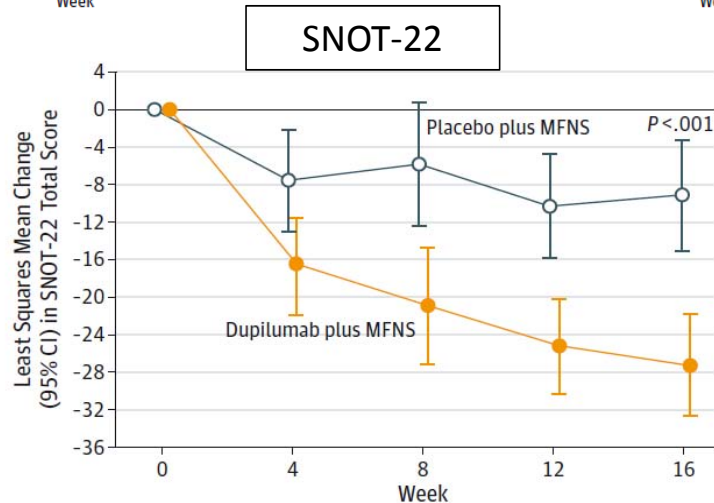
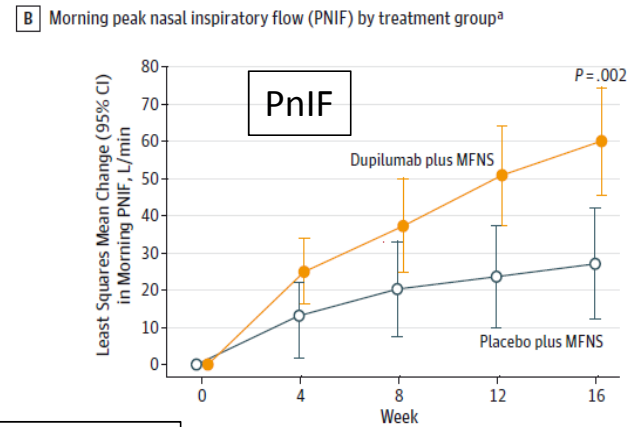
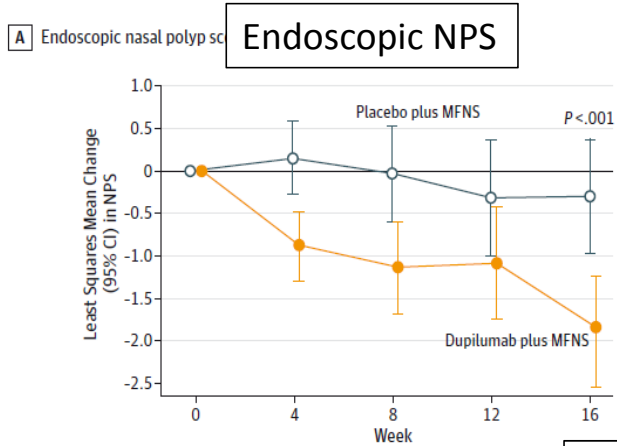
Asthma patients (~50%) had to have FEV1  $> 60\%$  predicted, ICS dose  $\leq 1000 \mu\text{g}$ , no systemic steroids or hospitalization in 3 months

**Primary Efficacy End Point** =  $\Delta$  total endoscopic nasal polyp score (BL  $\rightarrow$  Week 16) [included independent, blinded review of video recordings]

**Secondary Efficacy End Points** =  $\Delta$  Lund-Mackay CT score, % maxillary sinus occupancy, SNOT-22, UPSIT, PnIF, Patient rated reports of nasal congestion or obstruction, anterior and posterior rhinorrhea, loss in sense of smell, nocturnal awakenings, and overall symptoms.

**Exploratory End Points in Asthma** = FEV1, ACQ5

# Phase II Dupilumab Trial Results



## Population Baseline: 30 (Placebo) vs. 30 (Tx)

- Age 47-50 years
- M>F (53-60%)
- 97-100% → White
- 53-63% → Asthma
- Endoscopic TPS: ~5.7-5.9
- Δ drop out rates: 23% (placebo) vs. 6% (treatment)

## Results

1. NPS score reduction: -1.9 vs. -0.3;  $P < 0.001$ 
  - 70% vs. 20% had at least 1 point reduction ( $P < 0.001$ )
  - 1<sup>st</sup> noticed by Week 4
2. Lund-Mackay CT score: -9.1 vs. -0.2;  $P < 0.001$
3. %Δ Maxillary Sinus: -36.4% vs. 4.2%;  $P < 0.001$
4. PnIF: 60.2 L/min vs. 27.1 L/min;  $P = 0.002$
5. SNOT-22 Reduction: 41 → 30 vs. 41 → 13;  $P < 0.001$
6. NPS if comorbid asthma: -2.3 vs. 0.02;  $P < 0.001$
7. Lung function improved numerically in comorbid asthma (~300ml vs. 100ml;  $P = 0.07$ )

# Dupilumab: Phase III Trials (LIBERTY NP SINUS-24 & SINUS-52)

**Phase III Trials;** 2 DBRCT; 276 (LIBERTY NP SINUS-24) and 448 (LIBERTY NP SINUS-52); Dose = no loading, 300mg every 2 or 4 weeks

(Bachert et al., *Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials*, Lancet, 2019)

**Structure:** See diagram.

- ❖ Treatment with mometasone furoate 100 mg each nostril twice daily during run-in and throughout

**Inclusion criteria:** Ages 18 or older, bilateral nasal polyposis refractory to intranasal steroids

❖ **Required:**

- systemic steroids in the past 2 years (or intolerance to systemic steroids) OR previous sinus surgery
- Total endoscopic nasal polyp** score  $\geq 5$  and a minimal 2 in each nostril
- $\geq 2$  of the following symptoms: nasal congestion or obstruction, and at least one other symptom: discharge, reduction or loss of sense of smell
- 50%** with AERD or asthma

**Exclusion criteria:** (1) biologic/ immunosuppressive treatment in last 2 months, (2) experimental monoclonal in last 6 months, (3) anti-IgE in last 130 days, (4) any nasal surgery in last 6 months, (5) previously part of a dupilumab trial, OR (6) antrochoanal nasal polyps, acute CRS, EGPA, CF, AFS, ciliary disease

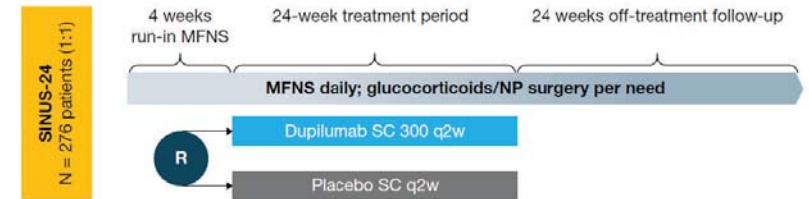
- Asthma patients with FEV1  $\leq 50\%$  predicted.

**Primary Efficacy End Point** =  $\Delta$  total endoscopic nasal polyp score AND nasal congestion severity (based on monthly average) [both NPS and Lund-Mackay CT scan scoring was done centrally by masked review of the video recordings]

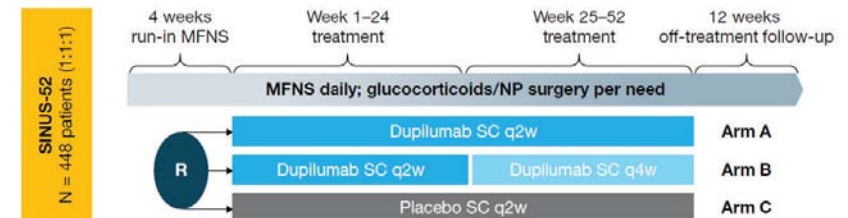
**Secondary Efficacy End Points** =  $\Delta$  Lund-Mackay CT score, a composite severity score, SNOT-22, UPSIT, reported loss of smell

## Study Designs

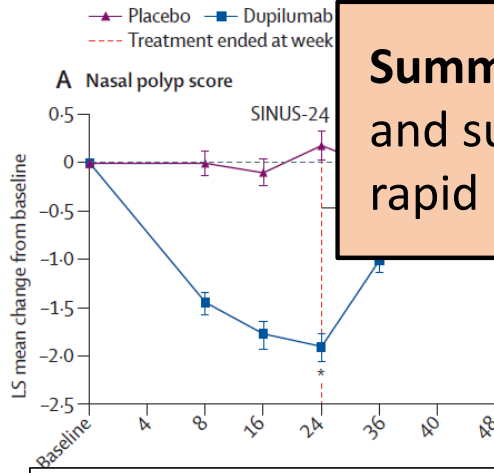
(A) SINUS 24



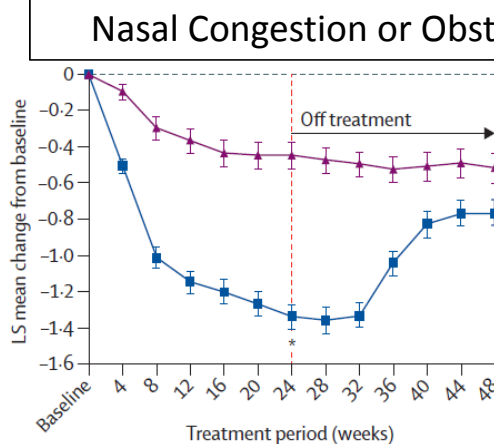
(B) SINUS 52



# Phase III Dupilumab Trial Results



**Summary:** Highly significant improvements in all objective and subjective measures ( $P < 0.0001$ ) on therapy with fairly rapid regression after discontinuing therapy.



**Results at Week 52**

**NPS (Scale 0-8):** -2.2 vs. 0.15 ( $\Delta = -2.4$ ;  $P < 0.0001$ )

**Nasal congestion or obstruction (Scale 0-3):** -1.35 vs. -0.37 ( $\Delta = -0.98$ ;  $P < 0.0001$ )

**SNOT-22:** -29.8 vs. -8.9 ( $\Delta = -20.96$ ;  $P < 0.0001$ )

to -1.9 vs. 0.2 to 0.1; (LS -1.8,  $p < 0.0001$ )

uction score: LS mean  $\Delta = -0.9$  9 (SINUS-52;  $P < 0.0001$ )

S-24); -5.1 (SINUS-52)\*

): -2.6 (S-24); -2.4 (S-52)\*

S-52)\*

-24); -1.0 (S-52)\*

Population Baseline

Results at Week 24

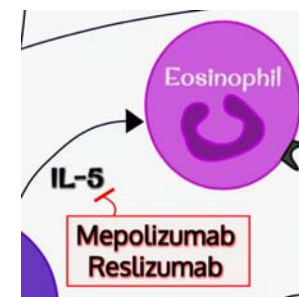
SNOT-22: -30.4 (S-24), -17.4 (S-52)\*

\* P-values all < 0.0001

(Bachert et al., Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials, Lancet, 2019)

# Mepolizumab: Phase II Data Supporting Efficacy; Phase III Trials Completed.

Mechanism	What it means?	FDA Approval
IL-5 = eosinophil development and survival; promotes airway inflammation. Mepolizumab, an IL-5 antibody, binds and removes IL-5 systemically.	Effectively reduces blood and tissue eosinophils. <ul style="list-style-type: none"> <li>❖ IL-5 has key role in NP pathogenesis.</li> <li>❖ NP are characterized by local eosinophilic inflammation.</li> </ul>	(1) Asthma (6 years and older) with an eosinophilic phenotype (100mg dose) (2) Adults with EGPA (300mg dose)



**Phase II Trial;** DBRCT; 105 total patients; Dose = 750mg IV every 4 weeks (only dose available at SoS)  
 (Bachert et al., *Reduced need for surgery in severe nasal polyposis with mepolizumab: Randomized trial*, JACI, 2017)

## Structure:

**Inclusion criteria:** Ages 18-70, severe recurrent bilateral nasal polyposis, 1 prior nasal surgery, refractory to steroids (at least 3 months of nasal steroids and 1 short course of oral steroids).

❖ Required surgery according to:

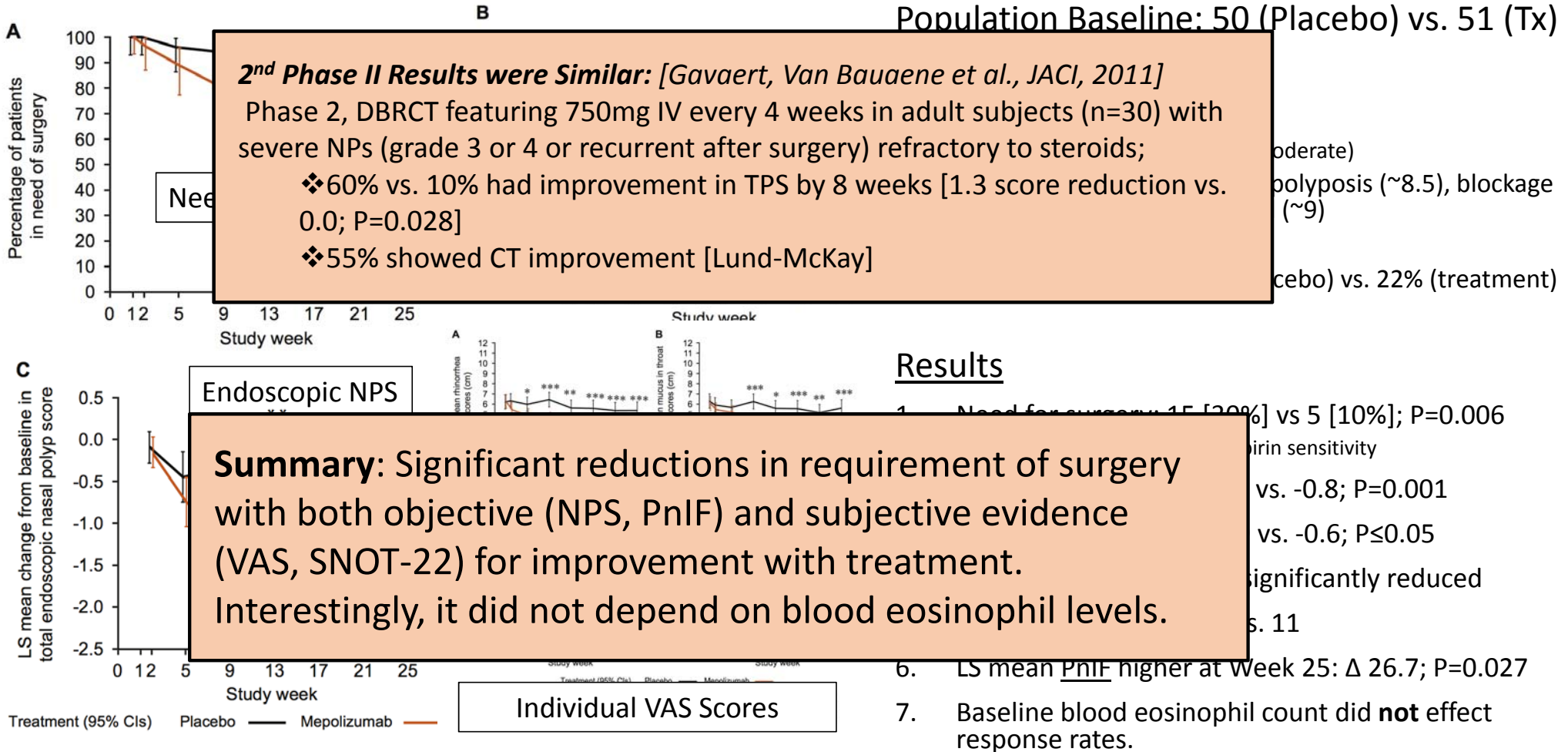
- ❑ (1) **endoscopic nasal polyp** score  $\geq 3$  in 1 nostril and minimal 2 on the other side AND
- ❑ (2) **VAS**  $> 7$  (how much trouble in each of the following: rhinorrhea, mucous in throat, nasal blockage, loss of smell)

**Exclusion criteria:** oral steroids continuously, recent biologics ( $\leq 12$  months), recent hospitalization for asthma ( $\leq 4$  weeks).

**Primary Endpoint** = no longer met criteria for surgery based on endoscopic nasal polyp score and VAS 4 weeks after final dose (Week 25).

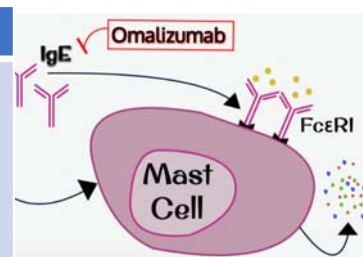
**Secondary Endpoints** = # meeting surgery criteria at each time point,  $\Delta$  VAS (total & individual; 25 weeks),  $\Delta$  TPS (25 weeks),  $\Delta$  SNOT-22 (25 weeks), EuroQual 5-Dimensions [EQ-5D] (25 weeks),  $\Delta$  PnIF, Sniffin' Sticks Screening-12, lung function, blood eosinophils and pharmacokinetics.

# Phase II Mepolizumab Trial Results



# Omalizumab: Phase II Efficacy Trial

Mechanism	What it means?	FDA Approval
Binds to the Fc region of IgE and blocks its binding to the high-affinity IgE receptor, FcεR1. Omalizumab reduces <i>free</i> IgE by 96%.	Effectively reduces IgE; reducing mast cell degranulation, IgE receptors and signaling effects on immune cells	(1) Moderate to severe persistent asthma (6 years and older) with a positive skin test or in vitro reactivity to a perennial aeroallergen (2) Chronic idiopathic urticaria in adults and adolescents 12 years of age and older



**Phase III Trial;** DBRCT; 24 total patients (23 treated); Dose = varied based on total IgE levels

(Gevaert et al., *Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma*, JACI, 2012)

**Structure:** 2-week run-in period; 2:1 randomization; 16 weeks of Tx; 20 weeks total

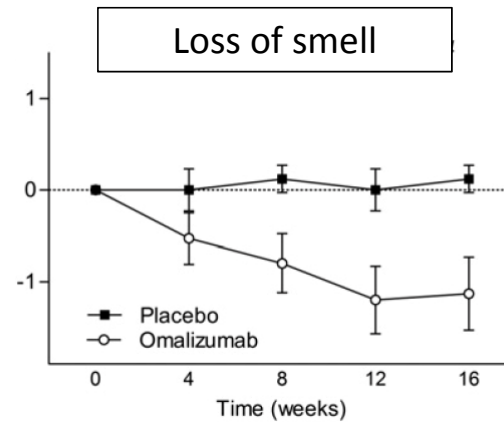
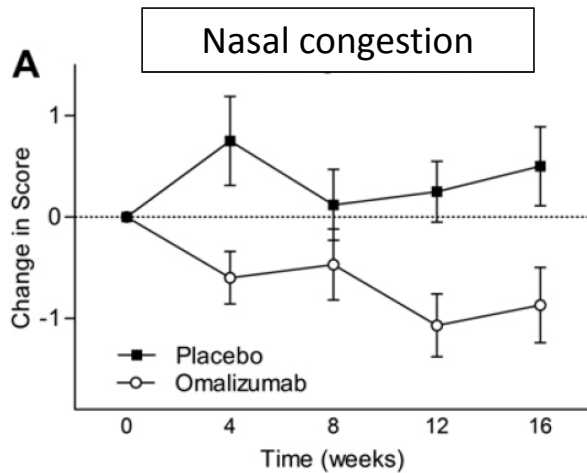
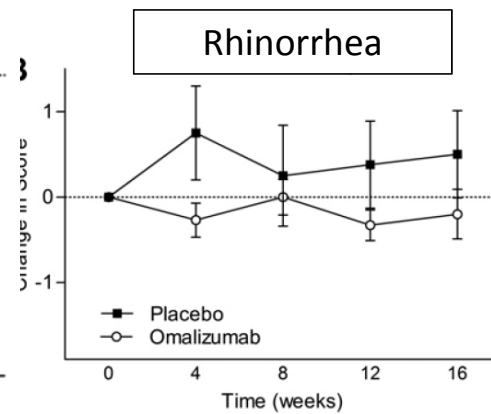
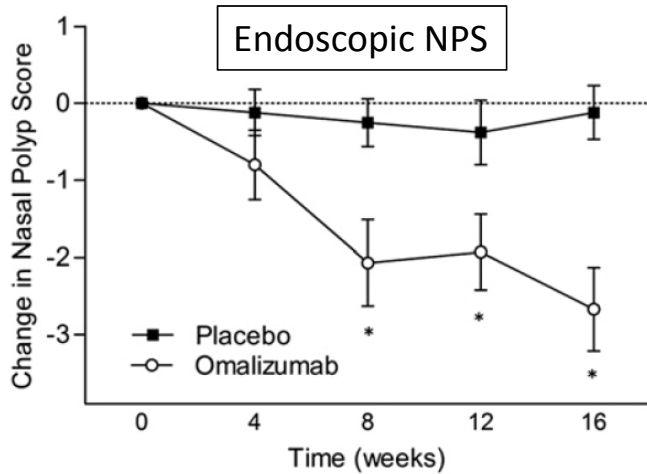
**Inclusion criteria:** Ages 18 and older with CRSwNP and comorbid asthma (based on GINA guidelines and diagnosed by a respiratory physician) for > 2 years and a **total IgE** between 30 and 700 kU/mL

**Primary Efficacy End Point** =  $\Delta$  total endoscopic nasal polyp score (BL  $\rightarrow$  Week 16)

❖ Note: Significant differences in polyp score grading noted from more recent scales.

**Secondary Efficacy End Points** =  $\Delta$  Lund-Mackay CT score, nasal and asthma symptoms, lung function testing, SF-36, RSOM-31. AQLQ

# Phase II Omalizumab Trial Results



## Population Baseline: 8 (Placebo) vs. 15 (Tx)

- Age 45-50 years; M>F (2:1)
- 50% aspirin sensitivity; 100% asthma
- 75-87% with prior sinus surgery
- TPS ~6; Lund-Mackay ~12
- FEV1 ~ 89-99%
- Eos = 390-475

## Results

1. NPS score reduction: -2.7 vs. -0.12; P=0.02
2. CT score: 17.6→13.6 (-4) vs. 17.8→18.3 (0.5)
3. QoL and Symptoms scores: UPSIT, AQLQ, SF-36, and symptoms of loss of smell, congestion, rhinorrhea, physical health and AQLQ



# Omalizumab: Phase III Trials (POLYP1 & POLYP2)

**Phase III Trial;** DBRCT; 138 (POLYP1) and 127 (POLYP2) total patients; Dose = varied based on total IgE levels

(Gevaert et al., *Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma*, JACI, 2012)

**Structure:** 5-week run-in period; 1:1 randomization; 24 weeks of therapy; 4-6.5% drop out rate; 4 week follow-up period

❖ Background therapy: Intranasal mometasone furoate

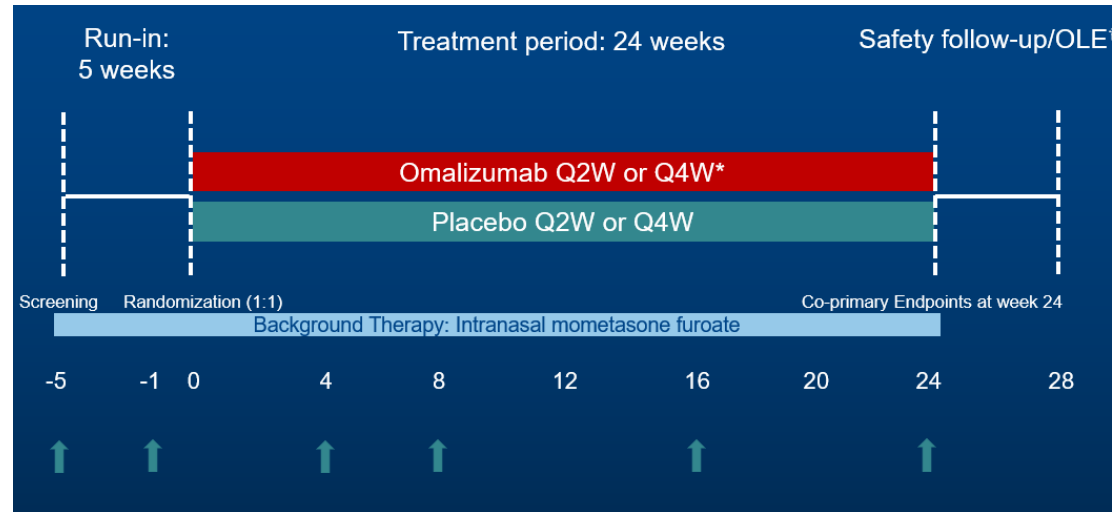
## Inclusion criteria

- ❑ NPS  $\geq 5$  with score of  $\geq 2$  for each nostril;
- ❑ SNOT-22 score  $\geq 20$  at baseline
- ❑ Treatment with nasal mometasone 200  $\mu\text{g}$  BID (or QD if intolerant to BID) during run-in, with  $\geq 70\%$  adherence
- ❑ Treatment with nasal mometasone  $\geq 200$   $\mu\text{g}$  QD (or equivalent of another INCS) for 1 month prior to first screening visit
- ❑ Nasal congestion score (NCS)  $\geq 2$  (with presence of nasal discharge and/or reduced smell) at first screening visit and weekly average NCS  $> 1$  at randomization
- ❑ Eligibility for dosing (i.e., serum IgE level  $\geq 30$  to  $\leq 1500$  IU/mL and body weight  $\geq 30$  to  $\leq 150$  kg at screening)

**Exclusion Criteria:** (1) Treatment with immunosuppressants, other than systemic steroids, in prior 2 months, (2) Nasal surgery in last 6 months, (3) Treatment with leukotriene antagonists/modifiers, unless stable dose for  $\geq 1$  months, (4) anaphylaxis/hypersensitivity to omalizumab, OR (5) Treatment with investigational drugs in past 12 weeks or monoclonal antibodies in past 6 months

❖ **Co-Primary Efficacy End Point** =  $\Delta$  total endoscopic nasal polyp score (BL  $\rightarrow$  Week 24);  $\Delta$  daily NCS (BL  $\rightarrow$  Week 24)

❖ **Secondary Efficacy End Points** =  $\Delta$  in total nasal symptoms score (TNSS), SNOT-22 and UPSIT (BL  $\rightarrow$  Week 24)

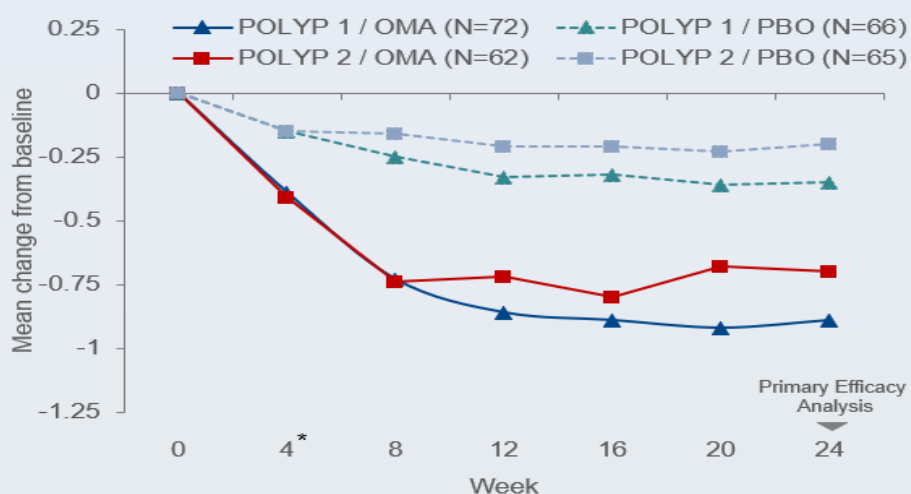


# Phase III Omalizumab Trial Results – Primary Efficacy End Points

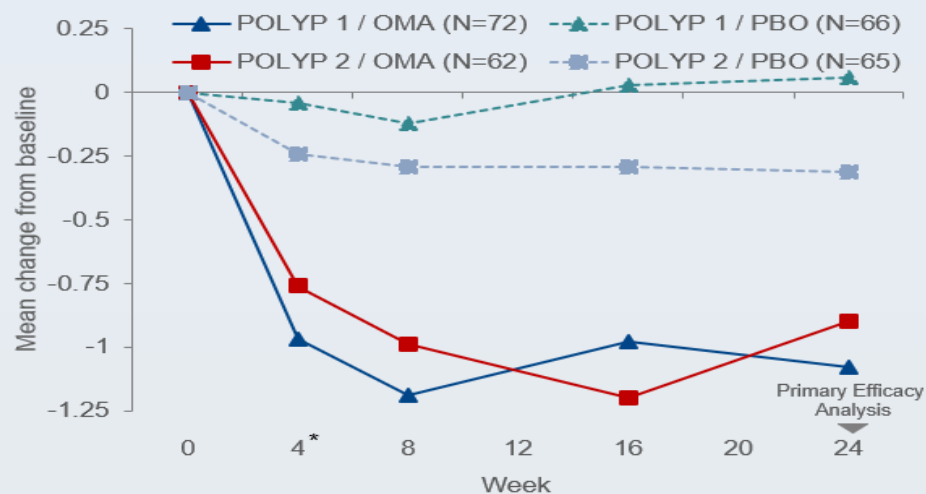
## Population Baseline:

- Age ~49-52 years; M>F (62-67%); 32-42% → Asthma (3-16% severe)
- Endoscopic TPS: ~6.1-6.3
- Eosinophil counts: 310-357 cells/ $\mu$ L

### Nasal Congestion Score



### Nasal Polyps Score



Mean change from baseline to Week 24

Nasal congestion score (NCS)  
Nasal polyps score (NPS)

Omalizumab

POLYP 1  
Placebo

P Value

Omalizumab

POLYP 2  
Placebo

P Value

Nasal congestion score (NCS)	-0.89	-0.35	0.0004	-0.70	-0.20	0.0017
Nasal polyps score (NPS)	-1.08	0.06	<0.0001	-0.90	-0.31	0.0140

**\*Placebo-controlled improvements in NCS and NPS were observed at Week 4 in both studies ( $P < 0.05$ , unadjusted for multiplicity)**

# Phase III Omalizumab Trial Results – Secondary Efficacy End Points

Mean Change From Baseline to Week 16	POLYP 1			POLYP 2		
	Omalizumab (n=72)	Placebo (n=66)	P value	Omalizumab (n=62)	Placebo (n=65)	P value
NCS at week 16 (0–3)	-0.89	-0.32	< 0.0001	-0.80	-0.21	< 0.0001
NPS at week 16 (0–8)	-0.98	0.03	< 0.0001	-1.20	-0.29	0.0002
Mean Change From Baseline to Week 24						
SNOT-22 (0–110)	-24.70	-8.58	< 0.0001	-21.59	-6.55	< 0.0001
Sense of smell score (0–3)						0.0024
TNSS (0–12)						< 0.0001
Patients with comorbid asthma AQLQ $\geq$ 0.5 (MCID), n (%)*						0.0396
Postnasal drip score (0–3)						0.0001
Runny nose score (0–3)	-0.77	-0.34	0.0023	-0.70	-0.08	< 0.0001
UPSIT smell assessment (0–40)	4.44	0.63	0.0024	4.31	0.44	0.0011
Pooled Outcome	Omalizumab (n=134)	Placebo (n=131)	P Value			
Required rescue treatment (SCS for $\geq$ 3 consecutive days or NP surgery), n (%)	3/129 (2.3%)	8/129 (6.2%)	0.1639			
	62.5% relative reduction in systemic steroid usage but with small number of steroid-requirement events and not statistically significant					

**Summary: Significant improvements in both objective and subjective measures on therapy with results observed as early as Week 4.**

Not significant per SAP or not included in the type 1 error control plan. AQLQ, asthma quality of life questionnaire; NCS, nasal congestion score; NPS, nasal polyps score; SNOT-22, sinonasal outcome test 22; TNSS, total nasal symptom score; UPSIT, University of Pennsylvania smell identification test.

## Future direction: Algorithm Development and Endotyping Efforts

Bachert, Zhang et al. *Endotype-drive care pathways in patients with chronic rhinosinusitis*, Clinical reviews in allergy and immunology, JACI, 2018.

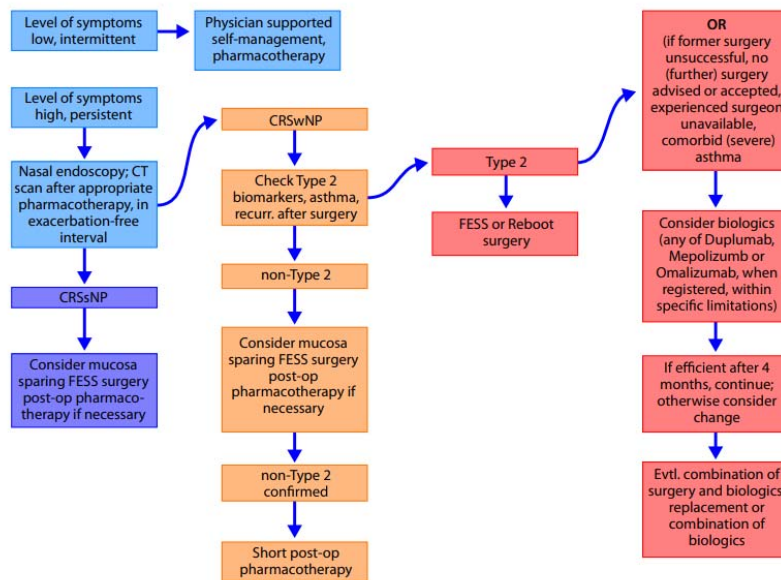
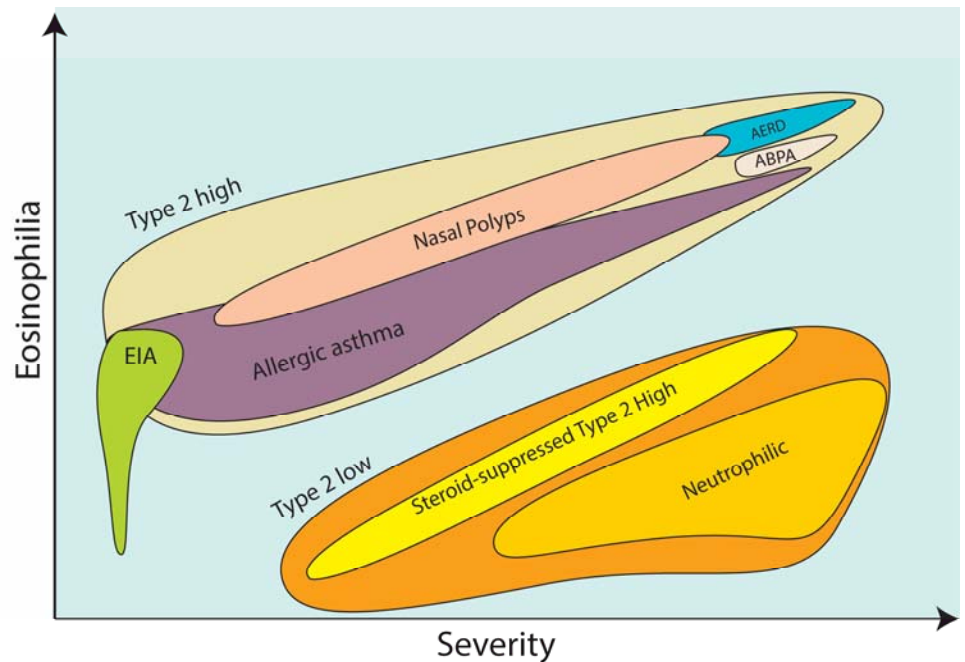


FIG 4. ICPs for CRS (regional differences and new studies can lead to changes of the ICP). FESS, Functional endoscopic sinus surgery.

### Type 2 'High' vs. Type 2 'Low':

Possible markers of Type 2 disease: Caucasian, comorbid asthma (early and late onset), history of atopic march, blood eosinophilia, high blood IgE, multiple positive skin tests or blood specific IgEs, sputum eosinophilia, high Type gene signature in airway epithelial cell brushings, AERD, recurrence after sinus surgery.



True or False?

For most patients, newer biologics are preferable to sinus surgery for the initial treatment of polyps because surgery costs more, it has higher morbidity, and is more than likely going to be unsuccessful anyway.

## True or False?

For most patients, newer biologics are preferable to sinus surgery for the initial treatment of polyps because surgery costs more, it has higher morbidity, and is more than likely going to be unsuccessful anyway.

**FALSE, surgery will likely be successful, and will be cheaper for most patients. Biologics will play a role in those with disease that is refractory to surgery and first line therapies.**

## Summary Statements

- Nasal steroids and **short** courses of oral steroids are the only Grade A recommendations, although it's common practice to recommend saline rinses.
- Antibiotics are more recommended with CRSsNP than CRSwNP.
- Dupilumab FDA-approved for CRSwNP
- Omalizumab Phase II and III trials were both positive.
- Mepolizumab Phase II trials positive, Phase III trial ended Dec. 2019
- With a ~60% success rate and costing ~\$15-20K, surgery likely the best first option prior to biologic therapy.
- If AERD, consider aspirin desensitization procedure & biologic therapy after nasal surgery.