Current State-of-the-Art of SLIT: Bench to Bedside

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Disclosures

In the past 3 years, I have received research grants from: Stallergenes-Greer, Circassia, Merck.

I am a consultant to: ASIT, Allakos, Allergy Therapeutics, Biomay, Stallergenes-Greer.

I am a section editor and author for UpToDate.

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SLIT-tablet Pivotal European & US Clinical Trials

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Pertinent Timothy Grass SLIT-tablet Seasonal Clinical Trials

a) Sublingual immunotherapy with once-daily grass allergen tablets: A randomized controlled trial in seasonal allergic rhinoconjunctivitis; Durham et al; J Allergy Clin Immunol 2006.

b) Efficacy and safety of sublingual immunotherapy with grass allergen tablets for seasonal allergic rhinoconjunctivitis; Dahl et al; J. Allergy Clin. Immunol. 2006.

c) Safety and efficacy in children of an SQ-standardized grass allergen tablet for sublingual immunotherapy; Bufe A, Eberle PO, Franke-Beckmann E, et al; J Allergy Clin Immunol 2009.

d) A phase 3 trial assessing the efficacy and safety of grass allergy immunotherapy tablet in subjects with grass pollen-induced allergic rhinoconjunctivitis with or without asthma. Murphy K, Gawchik S, Bernstein DI, et al. J Negat Results Biomed 2013.

e) Efficacy and safety of Timothy Grass Allergy Immunotherapy Tablet Treatment in North American Adults. Nelson HS, Nolte H, Creticos PS, et al; J Allergy Clin Immunol 2011.

f) Efficacy and safety of timothy grass allergy immunotherapy tablets in North American children and adolescents. Blaiss M, Maloney J, Nolte H, et al. J Allergy Clin Immunol 2011.

g) Efficacy and safety of grass sublingual immunotherapy tablet, MK-7243: a large randomized controlled trial. Maloney J, Bernstein DI, Nelson H, Creticos, PS, Nolte, et al. Ann Allergy Asthma Immunol 2014.

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Timothy Grass Sublingual Immunotherapy Tablet

[Grastek® (ALK-US); Grazax ® (ALK-Europe]

Indication:

Timothy grass pollen allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis/conjunctivitis

- confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies to timothy grass (Phleum) or cross-reactive grass pollens of the Temperate Family [Orchard (Dactylis) / Meadow Fescue (Festuca) / Ky Blue (Poa) / perennial Rye (Lolium) / Red Top (Panicum) / Sweet Vernal (Anthox)]

Dose/Administration:

- Single, 2800 BAU (~15 mcg Phl p 5) rapidly dissolving tablet administered SL (under the tongue), once daily to pts 5-65 yrs of age

-- pre/co-seasonal treatment (initiated 12 weeks prior to the expected pollen season and cont'd through the season)

-- perennial regimen (year-round therapy) for induction of sustained effect (based on 3-yr maintenance regimen demonstrating persistence of effect in subsequent grass season (one year after discontinuation of treatment)

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2004 European Cx Trial of Efficacy and Safety of Timothy Sublingual Tablet Immunotherapy for SAR in Adults; Dahl, Kapp, Colombo, et al; JACI 2006

Study Design:

- Longitudinal DBPC, parallel-group clinical trial
  n = 634 grass allergic adults
- Treatment: daily administration of Timothy SLIT [75,000 SQ-T (15 mcg Phl p 5; 2800 BAU)] vs Placebo; 16 wks pre-GPS

Entry Criteria:

- history of rhinoconjunctivitis in previous grass season
- + skin prick test to *Phleum pratense* (≥3mm wheal)
- + serum allergen-specific IgE [Class II (0.7 kU/L; by ImmunoCap)]

Outcomes:

Significant improvement in primary efficacy analysis vs placebo:
Rhinoconjunctivitis Symptom Score: 30% (p= 0.005); Medication Score: 38%.
[Improvement in secondary outcomes vs PL: well days (53% vs 44%; p < 0.0001), VAS score (12 vs 18; p < 0.001)]

Most frequent adverse events (Tx vs PL): oral pruritus (46% vs 4%); mouth edema (18% vs 1%); ear itch (12% vs 1%); throat irritation (9% vs 1%) [37% moderate; 5% severe]

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2012 Phase III Large-Scale Cx Trial of Efficacy and Safety of Grass Sublingual Tablet Immunotherapy in Children and Adults

Maloney, Bernstein, Nelson, Creticos, et al. Ann Allergy Asthma & Immunol 2014; 146:153

Study Design:

- Longitudinal DBPC, parallel-group clinical trial
  n = 1501 grass allergic children & adults (5-65 years old)
- Treatment: daily administration of Timothy SLIT [2800 BAU *Phleum pratense* (~15 mcg Phl p 5)] vs Placebo; 12 wks pre-GPS

Entry Criteria:

- history of AR/C with or without asthma in previous grass season
- + skin prick test to *Phleum pratense* (≥5mm wheal vs saline)
- + specific IgE against P pratense [Class II (0.7 kU/L; ImmunoCap)]

Outcomes:

Significant improvement in 1^0 outcome [TCS (med diff) : 23% vs PL (p<.001) (entire season)] // Improvement in secondary outcomes vs PL: $TCS_{(peak)}$: 29% (p<.001) ; DSS_{es}: 20% (p=.001) ; DMS_{es}: 35% (mn); (p<.001) ; $RQOL_{pk}$: 12%; (p=.027)

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Five-Grass Sublingual Immunotherapy Tablet

[Oralair® (Stallergenes-Greer)]

Indication:

5-grass pollen allergen extract indicated as immunotherapy for the treatment of grass pollen-induced allergic rhinitis/conjunctivitis

- confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies to any of the 5 grass species contained in the product: Timothy (Phleum) / Orchard (Dactylis) / Ky Blue (Poa) / Rye (Lolium) / Sweet Vernal (Anthox)]

Dose/Administration:

- single daily dose [300 IR] in adults (18-65 yrs); 3-day step-up dosing [100/200/300 IR] in children and adolescents (5-17 yrs) of a rapidly dissolving tablet administered SL (under the tongue)

-- pre/co-seasonal treatment (initiated 16 weeks prior to the expected pollen season and cont'd through the season)

-- not approved for perennial regimen (year-round therapy) for induction of sustained effect

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Pertinent 5-Grass SLIT-tablet Seasonal Clinical Trials

a) Optimal dose, efficacy, and safety of once-daily sublingual immunotherapy with a 5-grass pollen tablet for seasonal allergic rhinitis; Didier A, Malling H-J, Worm M, et al. J. Allergy Clin. Immunol. 2007; 120:1338-1345.

b) Efficacy and Safety of 5-grass pollen sublingual immunotherapy tablets in pediatric allergic rhinoconjunctivitis; Wahn U, Tabar A, Kuna P, et al. J. Allergy Clin. Immunol. 2009; 123:160-166.

c) Clinical efficacy of 300IR 5-grass pollen sublingual tablet in a US study: The importance of allergen-specific serum IgE; Cox LS, Casale TB, Nayak AS, et al J. Allergy Clin. Immunol. 2012; 130:1327-1334.

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Clinical Efficacy of 300IR 5-Grass Pollen Sublingual Tablet in a US Study: The Importance of Allergen-specific Serum IgE

Cox, Casale, Nayak, Bernstein, Creticos et al. JACI 2012; 130:1327-34.

Study Design:

- Randomized DBPC, parallel-group clinical trial
  n = 473 grass allergic adults (18-55 years of age)
- Treatment: daily administration of 300 IR 5-grass extract (timothy/orchard/rye/sweet vernal/bluegrass), or placebo; initiated 16 wks pre-season and maintained through the grass season

Entry Criteria:

- history of grass-induced rhinoconjunctivitis for ≥ previous 2 years
- retrospective RTSS ≥ 12 in prior grass season
- + skin prick test to timothy (flare: ≥10mm; wheal ≥ 5mm diameter)
  [patients excluded with symptoms due to confounding allergens]
- if asthmatic: FEV1 ≥ 80% and no controller medication use

[Timothy grass-specific serum IgE was measured on all subjects but was not an entry criterion into the study]

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Five-Year Grass SLIT Studies

· Sublingual grass allergen tablet immunotherapy provides sustained clinical benefit with progressive immunologic changes over 2 years. Dahl et al; J Allergy Clin Immunol 2008

· SQ-standardized sublingual grass immunotherapy: Confirmation of disease modification 2 years after 3 years of treatment in a randomized trial; Durham et al; J Allergy Clin Immunol 2012; 129:717-725.

· Sustained 3-year efficacy of pre- and coseasonal 5-grass-pollen sublingual immunotherapy tablets in patients with grass pollen-induced rhinoconjunctivitis. Didier A, Worm M, Horak F et al; J Allergy Clin Immunol 2011; 128:559-566.

· Results from the 5-yr SQ Grass SLIT-tablet asthma Prevention (GAP) trial in children w/ grass pollen allergy Valovirta E et al; J Allergy Clin Immunol 2018; 141:529-538.

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Confirmation of Disease Modification 2 Years after 3 Years of Grass AIT in a RCT. Durham, et al; JACI, 2008; 121: 512-18.

Study Design:

- Five-year longitudinal DBPC clinical trial of Timothy grass sublingual tablet IT (15µg Phl p 5) vs Placebo

  n= 241/634 grass allergic adult subjects evaluated for sustained efficacy in the 2 seasons following completion of 3-yr period of daily tx

Clinical Results:

- Weighted rhinoconjunctivitis combined score was reduced by 33/41/36% // 34/27%; p≤.003) vs placebo
  - -- Sustained reduction in mean rhinoconjunctival symptom score (31/36/29% // 26/25%; p≤.004) vs placebo
  - -- Sustained reduction in mean rhinoconjunctival medication score (38/45/40% // 29/20%; p≤.022; x Yr 5 NS) vs placebo
- Significant improvement in QOL; ↑ in symptom/med-free days
- Persistence of immunologic changes [IgG4 and IgE-blocking factor]

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Results from the 5-Yr SQ Grass SLIT-tablet Asthma Prevention (GAP) Trial in Children w/ Grass Pollen Allergy Valovirta et al; J Allergy Clin Immunol 2018; 141:529-538.

Study Design:

• Five-year longitudinal RDBPC clinical trial of Timothy grass SLIT-tablet (15µg Phl p 5) vs Placebo

n= 812 grass allergic children (5-12 yrs) evaluated for sustained efficacy in the 2 seasons following completion of 3-yr period of daily tx

Clinical Results:

- Treatment w/ the grass SLIT-tablet reduced the risk of experiencing asthma symptoms or using asthma meds at trial's end, during the 2-yr follow-up (off tx), and over the 5-yr course of the study (Odds Ratio:0.66; p<.036)

  - Tx imparted long-term clinical benefit (22-30%; p<.005 vs PL for all 5 yrs)
  - Tx reduced need for rhinoconj meds in SLIT group (27%; p<.001 vs PL; Yr 5)
  - Total IgE/grass-sIgE/grass $sIgG_4$/grass SPT each favorably Δ vs PL

- In contradistinction, no difference was observed in 1^0 Endpoint [time to onset of asthma (as defined by FEV^1 reversibility)]

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Two-Year Grass SLIT Study

a) Effect of 2 years of treatment with sublingual grass pollen immunotherapy on nasal response to allergen challenge at 3 years among patients with moderate-severe seasonal allergic rhinitis; Scadding GW, Calderon MA, Shamji MH, et al; JAMA 2017; 317:615-625.

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Benefit of 2 Years Grass SLIT on Nasal Allergen Provocation at 1-Year off Treatment Scadding et al; JAMA 2017

Study Design

Randomized DBPC clinical trial assessing the benefit of 2 years of grass SLIT vs PL in grass allergic patients with moderate-to-severe seasonal allergic rhinitis

n = 106 grass allergic patients with moderate-to-severe seasonal allergic rhinitis undergoing nasal allergen provocation at baseline and at 1st and 2nd year of treatment and at 1-year off treatment (Yr 3)

Treatment Regimen

- Grp A: 36 pts recv'd 15 µg Phl p 5 SLIT daily + monthly PL injections x 2 yrs
- Grp B: 36 pts recv'd 20 µg Phl p 5 SCIT monthly + daily PL tablets x 2 yrs
- Grp C: 34 pts recv'd matched double placebo

Results

1) Primary Endpoint [Nasal response to allergen challenge at year 3 (1-yr off tx)] showed no difference between SLIT and PL

2) No difference in secondary cx endpoints for SLIT or SCIT vs PL for PNIF/RQLQ/VAS

Conclusion

In patients w/ moderate-to-severe SAR, two years of grass SLIT was not able to demonstrate a persistence of positive effect in nasal response to allergen challenge

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Five-Year Grass Subcutaneous Immunotherapy (SCIT) Study

- Citation: Long-term Clinical Efficacy of Grass Pollen Immunotherapy.
  Durham SR, Walker SR, Varga E-M, et al; NEJM 1999; 341:468-475.

Study Design

Randomized DBPC clinical trial (n = 32 previously immunized patients)
- Grp A: cont'd maintenance grass immunotherapy (n=16)
- Grp B: randomized to placebo (n=16) [Discontinuation Grp]
- Newly recruited control patients (n = 15)
  (This matched control group did not receive injections)

Treatment Regimen

Standardized $AL[OH]_3$ depot grass pollen vaccine (Alutard SQ, ALK Abelló)
- 100,000 SQ units (20µg phleum allergen P5)/ml

Placebo injections
- identical diluent vials with $AL[OH]_3$ 0.01 µg of histamine/ml

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Maintenance schedule
- monthly [1ml] maintenance injections x3 years
- dose cut 40% during pollen season

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Conclusions

- Maintenance grass immunotherapy [3-4 years] induced prolonged clinical remission:
  - no significant differences observed in clinical outcomes between patients who continued immunotherapy and the discontinued patient group
  - clinical scores in both treated groups were markedly lower than those in the control (non-immunized) group
  - sustained reductions were observed in immunologic parameters
    - Late phase skin test response
    - CD3+ T-cell infiltration
    - IL-4 mRNA expression

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Ragweed Sublingual Immunotherapy Tablet

[Ragwitek® [ALK (US)]

Indication:

Short ragweed pollen allergen extract sublingual tablet is indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis

- confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies against short ragweed pollen

Dose/Administration:

- Single, 12 Amb a 1-Unit, rapidly dissolving tablet administered SL (under the tongue), once daily to pts 5-65 yrs of age

-- pre/co-seasonal treatment (initiated 12 weeks prior to the expected pollen season and cont'd through the season)

-- the drug was studied in patients with or without concomitant milder allergic asthma (studies allowed patients on daily low-dose inhaled corticosteroid therapy).

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Pertinent Ragweed SLIT-tablet Clinical Trials

a) Efficacy and safety of Timothy grass allergy immunotherapy tablet treatment in North American adults; Nayak AS, Atiee GJ, Dige E, et al; Allergy Asthma Proc 2012.

b) Randomized controlled trial of a ragweed allergy immunotherapy tablet in North American and European Adults; Creticos PS, Maloney J, Bernstein, DI, et al; J Allergy Clin Immunol 2013; 131:1342-1349.

c) Randomized controlled trial of ragweed allergy immunotherapy tablet efficacy and safety in North American adults; Nolte H, Hebert J, Berman G, et al. Ann Allergy Asthma Immunol 2013; 110:450-456.

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Ragweed Sublingual Immunotherapy Tablet

[Ragwitek® (ALK)]

Indication:

Ragweed pollen allergen extract indicated as immunotherapy for the treatment of short ragweed pollen-induced allergic rhinitis with or without conjunctivitis

- confirmed by positive skin test or in-vitro testing for pollen-specific IgE antibodies to short ragweed

Dose/Administration:

-- Single, 12 Amb a 1-unit rapidly dissolving tablet administered SL (under the tongue), once daily

-- pre/co-seasonal treatment (initiated 12 weeks prior to the expected pollen season and cont'd through the ragweed season)

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Phase III N. Am. Cx Trial of Efficacy and Tolerability of Ragweed Allergy Tablet Immunotherapy in Adults

Creticos P, Maloney J, Bernstein, et al; JACI 2013; 131:1342-49

Study Design:

- Longitudinal DBPC, parallel-group clinical trial
  n = 784 ragweed allergic adults
- Treatment: daily administration of ragweed AIT (1.5, 6, 12 Amb a 1 u AIT), or placebo; initiated 16 weeks pre-RW season

Entry Criteria:

- history of ragweed-induced rhinoconjunctivitis of 2 years duration
- + skin prick test to *Ambrosia artemisiifolia* (≥5mm wheal)
- + serum allergen-specific IgE [Class II (0.7 kU/L; by ImmunoCap)]

Outcomes:

Dose-dependent treatment effect observed for primary outcome [TCS: 1.5 Amb a 1-u 9%; p=.22); 6 Amb a 1-u AIT (19%; p=.01); 12 Amb a 1-u AIT (24%; p=.002) vs PL

Improvement in secondary outcomes: DSS [5/9/18%* (p=01*)]; DMS [16//35*//36%* (p<0.006*)] vs PL

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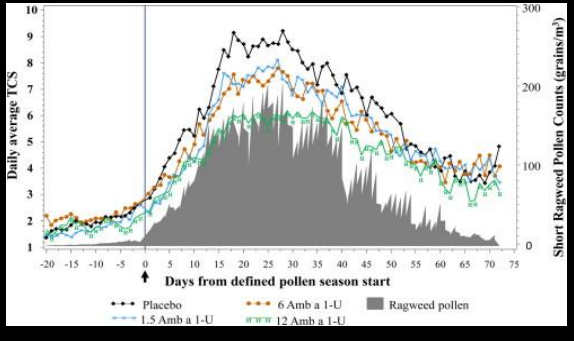
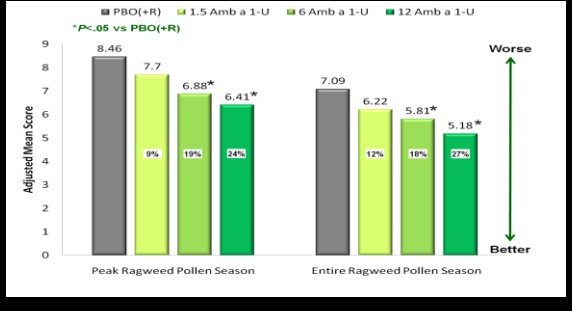
Graphic of Total Combined Score (TCS) Plotted Against Daily Average Pollen Count Over Course of Ragweed Season



Placebo
1.5 Amb a 1-U
6 Amb a a-U
12 Amb a 1-U

Reduction in TCS During Peak and Entire Ragweed Season Relative to Placebo



1.5 Amb a 1-u;
6 Amb a 1-u;
12 Amb a 1-u;
RW AIT
vs placebo

Creticos PS, Maloney J, Bernstein DI, et al; JACI 2013; 131:1342-49.

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Summary of Clinical Findings

- Immunotherapy with a dissolvable sublingual ragweed tablet resulted in significant dose-dependent therapeutic efficacy when compared to placebo
- Treatment induced a measurable immunologic response in IgG4 antibody against ragweed
- Treatment was generally well-tolerated
  - -- the majority (96%) of TRAEs were mild or moderate in severity
  - -- the most common TRAEs were throat irritation (12-21% vs 4%), oral pruritus, (5-14% vs 1%), ear pruritus (7-13% vs 1%), tongue edema (4-8% vs 1%)
- No anaphylaxic shock, systemic allergic reactions, tx-related SAEs, or asthma exacerbations were observed during the study

[1 almond-allergic subject self-administered Epi due to accidental ingestion of almonds]

- Discontinuations due to treatment-emergent adverse events were infrequent (5%; 8%; 8% vs 3% on placebo) [tongue edema was the most frequent AE leading to patient discontinuation]

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House Dust Mite Sublingual Immunotherapy Tablet

[Odactra™ [ALK (US)]

Indication:

House dust mite allergen extract sublingual tablet indicated as immunotherapy for the treatment of HDM-induced allergic rhinitis with or without conjunctivitis

- confirmed by *in vitro* testing for IgE antibodies to Dermatophagoides farinae or Dermatophagoides pteronyssinus HDM species or positive skin tests to licensed house dust mite extracts

Dose/Administration:

- Single, 12 SQ-HDM tablet, rapidly dissolving tablet administered SL (under the tongue), once daily to patients 18-65 yrs of age

* the drug was studied in patients with or without concomitant allergic asthma (studies allowed patients that met GINA Step 1/ Step 2 into the clinical trials (≤ low-moderate dose daily ICS therapy).

* contraindicated in patients with severe, unstable, or uncontrolled asthma

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Pertinent HDM SLIT-tablet Clinical Trials

- Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized DBPC Phase III trial. [MERIT Study] Demoly P, Emminger W, Rehm D, et al. J Allergy Clin Immunol 2015.
- Virchow J, Becker V, Kuna P, et al. Efficacy of a HDM sublingual allergen immunotherapy tablet in adults with allergic asthma: A randomized clinical trial. Virchow JC, Backer V, Kuna P, et al. JAMA 2016.
- Efficacy of house dust mite sublingual immunotherapy in North American adolescents and adults in a randomized placebo-controlled trial. Nolte H, Bernstein DI, Nelson H, et al. J Allergy Clin Immunol 2016.
- Efficacy & Safety of SQ HDM SLIT Tablet in Japanese Adults & Adolescents w/ HDM-induced Allergic Rhinitis. Okubo et al. J Allergy Clin Immunol 2016.
- HDM SLIT Tablet is Effective & Safe in Patients w/Allergic Rhinitis. Okamoto et al. Allergy 2017.

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Studies of Immunotherapy with Sublingual HDM Tablets

• **Demoly P, Emminger W, Rehm D, et al. Effective treatment of house dust mite-induced allergic rhinitis with 2 doses of the SQ HDM SLIT-tablet: Results from a randomized DBPC Phase III trial. J Allergy Clin Immunol 2016 [MERIT Study]**

Design: 992 European HDM-allergic patients with moderate-to-severe AR not well-controlled on meds Treatment Phase: randomized to 12 SQ-HDM vs 6 SQ-HDM vs PL over 1 year

Primary outcome: 12 SQ-HDM dose significantly reduced TCS during efficacy period (last 8 wks of treatment (18-22%; from 14 wks onward) [p=0.001; 0.002] Improvements also in 2^0 endpoints.

• **Virchow J, Becker V, Kuna P, et al. SQ HDM SLIT-tablet is effective in the treatment of allergic asthma: Results from a DBPC Phase III trial (MITRA). JAMA 2016.**

Design: 834 European HDM-allergic patients not well-controlled on ICS randomized in a DBPC fashion to receive 12 vs 6 SQ-HDM units or PL (in addition to ICS +/- SABA) / evaluated over 7-12 months during which ICS use was reduced by half x 3 months and subsequently withdrawn for next 3 months

Primary outcome: 12 SQ-HDM dose significantly reduced the risk of moderate-to-severe asthma exacerbations relative to PL (~34% risk reduction)

-- 36%↓ in risk of nocturnal awakenings or increase in daily symptoms
-- 48% reduction in risk of increased SABA use
-- 42% reduction in deterioration of lung function

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N. American Study of Immunotherapy with Sublingual HDM Tablet

• **Nolte H, Bernstein DI, Nelson H, et al. Efficacy of house dust mite sublingual immunotherapy in North American adolescents and adults in a randomized placebo-controlled trial. J Allergy Clin Immunol 2016; 138:1631-38.**

Design: 1482 subjects (aged: 12-65) with HDM-induced AR/C with or without asthma were randomized to daily SQ HDM SLIT-tablet (12 SQ-HDM dose) or placebo for up to 52 wks

Primary outcome (average TCRS; defined as rhinitis DSS + rhinitis DMS during the last 8 wks of treatment): 12 SQ-HDM dose significantly improved the *TCRS* by 17% ($p<0.001$; 95% CI: 10-25%) vs placebo during the efficacy period.

Asthma efficacy outcome (least-square mn asthma DSS): the12 SQ-HDM dose improved the *Asthma DSS* by 19% ($p<0.002$; between tx diff) [in subjects w/ reported asthma, a 25% tx diff was observed [95% CI: -0.46 (-0.83 to -0.10)].

Safety: most common AEs: throat irritation (67 vs 22%); oral pruritus (62 vs 14%); ear pruritus (51 vs 11%); lip swelling (18 vs 2%); swollen tongue (16 vs 2%); pharyngeal edema (14 vs 3%) [med onset: 1-8 days; med duration: 14-67 mins]

- 7 pts received Epi (3 in active tx grp) / No tx-related SAEs / No serious asthma events

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N. Am/European Study of Sublingual HDM Tablet (Stallg/Greer)

•**Efficacy & Safety of Sublingual Tablets of House Dust Mite Allergen Extracts in Adults and Adolescents with HDM-associated Allergic Rhinitis**

Design: Phase III RDBPC clinical trial
n=1607 subjects (aged: 12-65) with HDM-induced AR/C with or without asthma were randomized to daily SQ HDM SLIT-tablet (300IR) or PL x 1 year

Primary Outcome [TCS (Total Combined Score): sum of the patient's daily Rhinitis Total Symptom Score (RTSS) + daily Rescue Medication Score (RMS) assessed during the 4 weeks at the end of the 12-month treatment duration

Secondary Outcome Measures: Adverse events; safety and tolerability

Top Line Results:
- The study achieved its primary efficacy endpoint ($p<0.0001$)
- safety profile comparable to that observed in their other clinical studies with the HDM tablet
- Full data will be presented at the 2019 EAACI meeting

Sources: extrials.gov; company press release (11-20-2018) as mandated by Sarbanes-Oxley Transparency Act

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What's Next on the Horizon: Sublingual Tree Tablet (ALK)

- Status: submitted to European regulatory agency in 2018: status pending
  - the Tree SLIT-tablet is being developed as allergen IT for treatment of ARC induced by pollen from the birch tree homologous group
  - Dose: 12 DU as a rapidly dissolving SL tablet administered once daily; initiated 12 weeks pre-tree season
- Phase I Safety Study
  - demonstrated tolerability profile suitable for doses up to 12 DU
- Phase 2 European Trial [RDBPC; n=637 pts w/ mod-severe birch ARC]
  - evaluated doses of 0.5-12 DU: +DRC: > 4DU; induced IgG4
- Phase 2b Environmental Exposure Chamber Study
  - RDBPC trial (n=219) in subjects with moderate-severe birch ARC
  - designed to define optimal dose; also investigated efficacy of tablet against white oak (birch homologous tree pollen)
- Clinical Efficacy & Safety Field Trial
  - European Pivotal clinical trials completed; BLA submitted to European Regulatory

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Birch SLIT-tablet Reduces Symptoms of Allergic Rhinoconjunctivitis Triggered by Birch & Oak Pollen in the EEC

- Study Design: DBPC Environmental Exposure Chamber trial design
  - 219 adults with + skin prick test to birch and + specific IgE to birch major allergen (Bet v 1) at $\geq$ 0.7 kU/L
  - clinical history of moderate-to-severe rhinoconjunctivitis induced by pollen from birch homologous species (alder, hazel, hornbeam, oak)
- Treatment: 2 DU; 7 DU; 12 DU Birch pollen extract administered as an oral lyophilized (freeze-dried SL tablet) or Placebo
- Challenge methodology: baseline birch EEC session; re-challenge at 8/16/24 weeks; oak challenge at 24 weeks
- Results:
  - birch SLIT-tablet treatment resulted in significantly lower TSS during the 24-wk birch EEC session for both the 7 DU and 12 DU doses [%RD: 24% & 25% vs Placebo (p=.003; .002)]
  - birch SLIT-tablet treatment also positively impacted sensitivity to oak at the 24-wk EEC challenge [TSS %RD vs PL: 24% (p=.003)]
  - IgE and IgG4 assays supported these findings and demonstrated cross-reactivity to homologous birch species

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Studies of Immunotherapy with Sublingual Drops

- **In the United States, SLIT liquid/aqueous extracts (i.e., drops) are not FDA-approved; however, the "*off-label*" use of aqueous extracts (that are currently approved for use with subcutaneous immunotherapy) is being administered by increasing numbers of U.S. physicians.**

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Selected Clinical Studies with SLIT-drops: Ragweed

- A Double-blind, placebo-controlled evaluation of sublingual immunotherapy with a standardized ragweed extract in patients with seasonal allergic rhinitis. Andre et al. Int Arch Allergy & Immunol 2003.
- Canadian trial of sublingual swallow immunotherapy for ragweed rhinoconjunctivitis. Bowen et al; Ann Allergy Asthma Imm 2004.
- Sublingual immunotherapy in patients with allergic rhinoconjunctivitis caused by ragweed Pollen. Skoner et al. J Allg Clin Immunol 2010.
- Randomized, DBPC trial of standardized ragweed sublingual-liquid immunotherapy for allergic rhinoconjunctivitis. Creticos et al. J Allg Clin Immunol 2014.

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Phase III Randomized DBPC Trial of Standardized RW Sublingual-Liquid Immunotherapy for Allergic Rhinoconjunctivitis

Study Design:

- Randomized, double-blind placebo-controlled trial
  - [n = 429 ragweed allergic patients; 18-55 years age]

Entry Criteria:

- ≥ 2-year history of fall seasonal rhinoconjunctivitis +/- mild asthma
- + puncture skin test to ragweed (≥ 60mm sum of erythema)

Immunotherapy Phase

- Rush-dose escalation started 8-10 weeks preseason and continued through ragweed season

Results:

- improvement demonstrated for primary endpoint (TCS: symptom + medication use score) : 43% reduction relative to placebo ($p<0.001$) [ITT]
- Generally well-tolerated
  - no serious adverse events attributable to SLIT
  - no anaphylaxis

[Creticos et al. J Allg Clin Immunol 2014; 133:751-58]

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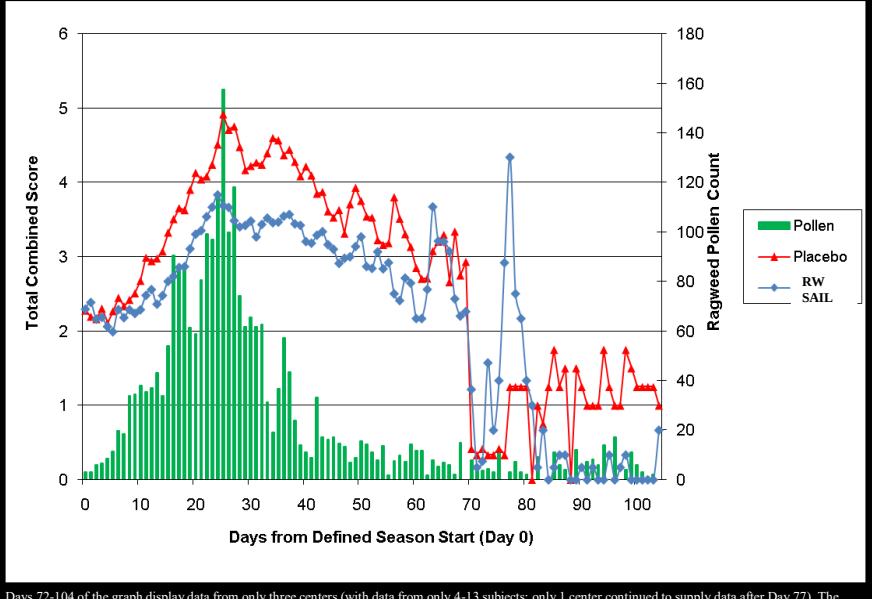
Mean TCS During the Entire Ragweed Pollen Season



Days 72-104 of the graph display data from only three centers (with data from only 4-13 subjects; only 1 center continued to supply data after Day 77). The uptick in TCS seen in the ragweed SAIL arm of the study on Days 76-79 is comprised of data from only 3–6 subjects on active treatment who recorded symptoms. SAIL=sublingual allergen immunotherapy liquid extract. [Creticos et al. J Allg Clin Immunol 2014; 133:751-58]

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Summary of Clinical Findings

- Sublingual immunotherapy with a standardized glycerinated ragweed liquid extract resulted in significant and clinically meaningful therapeutic efficacy when compared to placebo

  -- 43% reduction in TCS relative to PL (Δ from baseline for TCS: 0.82 (RW-SAIL) vs 1.44 PL (mean) [diff LS means, –0.83 (95% CI, –1.30 to –0.37); *p*<0.001]

- Treatment induced a measurable immunologic response in IgG4 antibody against ragweed

- Treatment was generally well-tolerated

• 94% of subjects achieved maximum-tolerated dose (mn: 50 Amb a 1 Units)

-- the most common TEAEs were headache (8 vs 9%), URI (5 vs 10%), GI (8 vs 6%)
-- the majority (95%) were mild or moderate in intensity

• tx-related local site rxs (oral pruritus; mouth pain; swelling) - transient and self-ltd [10% vs 2% in PL group] // no anaphylaxis observed in study

• only 2% of patients dropped-out due to adverse events

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Selected Clinical Studies with SLIT-drops: Other Allergens

· Response to sublingual immunotherapy with grass pollen extract: Monotherapy vs combination in a multiallergen extract. Amar et al; J Allg Clin Immunol 2009.

· High-dose SLIT with aqueous grass pollen extract in children. Wahn, Klimek, Ploszczuk et al JACI 2012.

· Sustained efficacy & safety of a 300IR daily dose of a SL solution of birch pollen allergen extract in adults with ARC: Results of a DBPC study. Worm, Rak, Blay, Malling, Melac, Cadic, Zeldin. Cx & Trans Allergy 2014.

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Sublingual Immunotherapy Comparisons

▪ Efficacy of sublingual immunotherapy with grass allergens for seasonal allergic rhinitis: A systematic review and meta-analysis.
DiBona D, Plaia A, Scafidi V, et al; J Allergy Clin Immunol 2010.

• MEDLINE search (1995-2010): 19 RDBPC trials (SLIT-drops; SLIT-tablets) that compared SLIT to PL (2971 pts) in patients with seasonal allergic rhinitis to grass

• SLIT w/ grass allergens resulted in a significant, but modest improvement in both symptoms (-0.32; 95%CI, -0.44 to -0.21) and medication usage [-0.33; 95%CI, -0.50 to -0.16] vs PL

▪ Efficacy of grass pollen allergen sublingual immunotherapy tablets for seasonal allergic rhinitis: A systematic review and meta-analysis.
DiBona D, Plaia A, Scafidi V, et al; J Allergy Clin Immunol 2015.

• MEDLINE/EMBASE/Cochrane (to 2014): 25 RDBPC trials [13 evaluated symptom score (4659 pts); 12 evaluated medication score (4558 pts)] in grass allergic pts treated with SLIT-tablets for seasonal allergic rhinitis

• SLIT w/ grass allergens resulted in a small benefit in reducing symptoms (-0.32; 95%CI, -0.44 to -0.21) and decreasing symptomatic medication usage [-0.33; 95%CI, -0.50 to -0.16] compared to placebo in the treatment of seasonal allergic rhinitis

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Systematic Reviews/Meta-analyses of SCIT & SLIT

▪ Efficacy of SCIT and SLIT with grass allergens for seasonal allergic rhinitis: A meta-analysis-based comparison.
DiBona D, Plaia A, Leto-Barone MS, et al; J Allergy Clin Immunol 2012.

▪ SCIT and SLIT for seasonal allergic rhinitis: A systematic review and indirect comparison. Dretzke J, Meadows A, Novielli, et al. J Allergy Clin Immunol 2013.

▪ Network meta-analysis shows commercialized subcutaneous and sublingual grass products have comparable efficacy.
Nelson H, Cartier S, Allen-Ramey F, et al; J Allergy Clin Immunol Pract 2015.

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Treatment Effect of Immunotherapy and Pharmacotherapies Relative to Placebo

- Treatment effect of subligual immunotherapy tablets and pharmacotherapies for seasonal and perennial allergic rhinitis: Pooled analyses. Durham SR, Creticos PS, Nelson HS, et al; J Allergy Clin Immunol 2016; 138:1081-1088.

- A meta-analysis of sublingual allergen immunotherapy and pharmacotherapy in pollen-induced seasonal allergic rhinoconjunctivitis. Devillier P, Dreyfus JF, Demoly P, Calderon MA. BMC Med 2014; 12:71.

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Compliance/Adherence in Immunotherapy

Real-life compliance and persistence among users of subcutaneous and sublingual allergen IT. Kiel MA, Roder E, Gerth van Wijk R, et al; JACI 2013;132:353-360.

- **Dutch pharmacy surveillance survey (1994-2009): 6486 patients started on HDM, grass, or tree IT (2796 SCIT; 3690 SLIT) [initiated by GP or specialist // drugs distributed at community pharmacy]**
  - **-- only 18% SCIT and 7% of SLIT patients achieved 3 years of IT [median duration: 1.7 yrs (SCIT); 0.6 yrs (SLIT)]**
  - **-- positive compliance: GP; older age; higher socioeconomic status**
  - **-- negative factors: cost; lifestyle; daily admin (SLIT); distance to office (SCIT)**

How adherent to SLIT rxs are patients? The manufacturers' viewpoint. Senna G, Lombardi C, Canonica GW, Passalacqua G. JACI 2010; 126:668-69 (Letter to the Editor)

- **Italian sales figures from two large manufacturers (acct for 60% of Italian IT market): sales decreases (Yr 1: 100% to 44%; Yr 2: 28%; Yr 3: 13%)**
- **No difference in d/c between SLIT for pollens vs HDM // modality of reimbursement of marginal relevance (in 2/3rd yrs) // control visits ?**

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