REGENERON
SCIENCE TO MEDICINE®

Immunology & Inflammation Areas of Interest

Dupilumab (IL4R)

(Investigator Initiated Studies and Research Collaborations)

DERMATOLOGY

Atopic Dermatitis:

Dupilumab in Atopic Dermatitis

- Evaluate the [optimal] utilization of dupilumab for the treatment of AD within the evolving therapeutic landscape, including dose modification & prompt treatment initiation
- Real world AD patient / disease characteristics, burden of AD and comorbid conditions
- Dupilumab use patterns, effectiveness, drug survival, and other attributes in real-world setting
- Special populations (e.g., very young AD patients, elderly, skin of color, mild to moderate AD, patients in which JAKi are inadvisable)
- Studies to measure the effect of dupilumab on AD symptoms and other important disease domains that are insufficiently characterized (sleep, circadian rhythms, pain, mental health, sensory processing, school performance, etc.)
- New mechanistic insights into dupilumab MOA, including effect on important inflammation markers in lesional and non-lesional skin not studied previously, new skin imaging techniques, new minimally invasive or non-invasive sample collection techniques, etc.
- Effect of dupilumab in AD patients with comorbid type 2 inflammatory diseases (e.g. AD with comorbid asthma ± allergic rhinitis ± food allergy, etc.)
- Effect of early AD treatment with dupilumab on the development of type 2 comorbidities, atopic march and disease-modifying aspects in general including bone health
- Effectiveness of dupilumab across different AD phenotypes and endotypes
- Establishing criteria for disease modification in AD

Disease State

- AD time course (natural history)
- New mechanistic insights into AD pathophysiology, including the identification of distinct phenotypes and endotypes

Epidemiology

- Prevalence of AD by gender, age group, age of onset, associated comorbidities, special populations
- Treatment patterns throughout the course of AD

Mechanistic

- Further understand the AD mechanism of disease, or dupilumab mechanism of action in relevant pathobiological contexts, such as,
- Pathobiology of IL4Ralpha in chronic itch
- Distinct role of IL-4/IL-13 vs. IL-13 alone
- IL4/IL13 signaling in fibrosis and skin remodeling
- Neuroimmune pathways in skin disease including itch

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DERMATOLOGY (Cont'd)

Other Dermatological Diseases

NOTE: For indications with ongoing clinical development programs, IIS proposals will typically be deferred until clinical development is complete and regulatory action is taken, unless it is determined that the IIS is complementary to the development program and necessary to support the regulatory submission.

Dermatology Indications - Dermatological Diseases Supported by Clinical Development – Prurigo Nodularis

Patient Population

- Epidemiology
- Natural history including disease progression
- Burden and unmet needs including limitations of current therapies

Pathogenesis

- Pathomechanistic relationship between PN and other comorbidities
- Pathogenesis including the role of IL4 and/or IL13, ~~and~~ mechanisms of itch and neuropathy, immune dysregulation
- Tissue remodeling and nodule formation
- Characteristics of lesional and non-lesional skin
- Exploration of PN and non-atopic PN in molecular, histopathological, and clinical profiles
- Cognitive dysfunction, neurobiological alterations in CNS

Clinical Practice

- Diagnosis and assessment of the disease severity, including biomarkers and imaging
- Disease endotypes and phenotypes
- Comorbidities including type 2, and impact of early treatment
- Special populations including skin of color and elderly

Dermatological Diseases Supported By Clinical Development – Chronic Spontaneous Urticaria

Patient population

- Epidemiology
- Natural history including disease progression
- Burden and unmet needs including limitations of current therapies

Pathogenesis

- Pathogenesis including the role of IL-4 and/or IL-13, mechanisms of itch and neuropathy
- Dupilumab mechanism of action in mast cell stabilization beyond IgE Barrier disruption and endothelial dysfunction
- Characteristics of lesional and non-lesional skin
- Cognitive dysfunction, neurobiological alterations in CNS

Clinical practice

- Diagnosis and assessment including biomarkers and imaging
- Disease endotypes
- Comorbidities including type 2
- Special populations including skin of color

Other Dermatological Diseases Supported By Clinical Development – chronic pruritus of unknown origin, bullous pemphigoid.

Patient population

- Epidemiology
- Natural history including patient journey and disease progression
- Burden and unmet needs including limitations of current therapies

Pathogenesis

- Pathogenesis including the role of IL-4 and/or IL-13 and mechanisms of itch and neuropathy
- The specific factors involved in the initial polarization toward Th2/type 2 inflammation (e.g., what is the primary source of IL-4?)
- Better understand the critical role of type 2 inflammation in BP pathophysiology, vs. the roles of type 1 and type 3 inflammation.
- Barrier disruption and tissue remodeling
- Characteristics of lesional and non-lesional skin

Clinical practice

- Diagnosis and assessment including biomarkers and imaging
- Disease endotypes
- Comorbidities including type 2 inflammatory comorbidities
- Special populations including skin of color and ICI-treated patients
- Clinical variants of pemphigoid (e.g., gestational)

Other Dermatologic Diseases beyond the diseases listed above where existing data suggest that IL-4 and/or IL-13 may play a central role (including pruritic skin diseases).

- Effect of dupilumab

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GASTROINTESTINAL (GI)

Eosinophilic Esophagitis (EoE): Mechanistic

- Advance understanding of the complex pathophysiology of EoE (barrier dysfunction, adaptive and innate immunity, inflammatory cells, remodeling and fibrosis)
- Elucidate endotype/phenotype heterogeneity in EoE

Eosinophilic Esophagitis (EoE): Disease State

- Explore predictive biomarkers of EoE disease progression and treatment response
- Investigate the advantages and limitations of alternate therapies
- Exploring definitions of disease control in EoE

Eosinophilic Esophagitis (EoE): Quality of Life

- Describe epidemiology and treatment patterns of EoE patients.
- Describe disease burden in different populations

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RESPIRATORY

Asthma – Mechanism of Action

- FeNO as prognostic/predictive biomarker
- Identifying novel response biomarkers
- Phenotyping/endotyping response
- Airway hyperresponsiveness
- Understanding the role of type 2 inflammation as driver of acute exacerbation
- Disease modification and airway remodeling
- Mucus plugging
- Small airways disease
- Role of dupilumab as disease modifying drug
- Prevention of lung function decline
- Understanding clinical relevance of remission on therapy
- Understanding airway barrier function and viral-medicated exacerbations
- Understanding and characterizing rapid response to dupilumab therapy

Asthma - Clinical and Observational Studies

- Understanding burden of disease
- Real world effectiveness
- Disease severity criteria
- Impact on inhaled therapy

Asthma - Comparative Data

- Efficacy in patients who switch biologics
- Indirect treatment comparisons among subpopulations
- OCS burden

Asthma - Special Populations

- Asthmatics with smoking history
- Obesity
- Exercise-induced asthma
- Efficacy in diverse populations
- Efficacy in underrepresented populations
- Patients with moderate asthma

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RESPIRATORY (Cont'd)

New Diseases Areas

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Other Respiratory Diseases

- COPD

Mechanism of Action

- Understanding role of type II inflammation in COPD
- Exploring definitions of disease modification in COPD
- Understanding role on mucus plugging
- Understanding role of type II inflammation in COPD exacerbations
- OMICS approaches to understanding COPD

Disease Burden

- Patient-centric endpoints (e.g. quality of life, sleep, depression, exercise tolerance, hospitalization, ER visits, mortality)
- Describing OCS and other treatment burden
- Describing healthcare utilization

Characterizing Patients

- Epidemiology (e.g. moderate-severe patients)
- Current and ex-smoker population
- Predictive biomarkers. FeNO (+eos) and novel biomarker investigation
- Understanding response to treatment
- Characterizing patients through endotyping/phenotyping
- Drivers of disease in non-cigarette smoking related disease (occupational and environmental exposure)
- Genetics and COPD. Clinical expression of genetic variants.
- Metabolomics and COPD.
- Effects of dupilumab in microbiome.
- Natural progression of diseases
- Cardiovascular comorbidities

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PEDIATRIC ASTHMA

Asthma Pediatrics: Mechanistic

- Airway Hyper Responsiveness
- Airway remodeling/Lung function decline
- Understanding and characterizing the role of T2 inflammation in driving disease
- Predictive T2 biomarkers for exacerbations and lung function
- Lung function “trajectory” across age groups
- Impact on growth and development
- Understanding remission on therapy
- Bone metabolism

Asthma Pediatrics: Clinical and Observational Studies

- Characterization of Pediatric Asthma population (biomarkers, lung function, OCS use)
- Burden of disease (patients and caregivers)
- Burden of OCS/ICS, including impact on growth
- Impact on inhaled therapy

Asthma Pediatrics: Comparative Data (direct or indirect); RWE Effectiveness; Special populations

- Allergic subtypes based on total/specific IgE and other type 2 biomarkers
- Underrepresented populations
- Associated atopic conditions
- Corticosteroids burst users
- Impaired lung function
- Switch from previous biologic

Asthma Pediatrics: Quality of Life

- Negative impact of severe asthma on patient/caregivers reported outcomes and on daily activities
- Benefit of dupilumab on patient/caregivers reported outcomes and on daily activities

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CHRONIC RHINOSINUSITIS WITH NASAL POLYPS (CRSwNP)

CRSwNP: Mechanism of Action

- Loss of sense of smell in CRSwNP and its diagnostic and prognostic value
- Role of Type 2 cytokines on CRSwNP development & progression
- Disease control, remission and/or modification in CRSwNP
- Prevention of nasal polyp regrowth and symptom recurrence in ~~and~~ relationship to surgery
- Relationship between type 2 inflammation and symptoms
- Sinus opacification in CRSwNP and predictive value of reducing opacification
- Role of Type 2 inflammation (including cytokines such as IL4, IL13 and inflammatory cells) in CRSwNP on disease burden such as nasal polyp formation (e.g. epithelial barrier function, mucus production), and loss of sense of smell
- Understanding neuroinflammatory pathways and potential impact of dupilumab
- Dupilumab impact on improving sleep, smell and taste in patients with CRSwNP
- Dupilumab efficacy/effectiveness on long-term outcomes such as surgery, oral steroid usage reduction

CRSwNP: Pathophysiology

- Role if IL-4 and IL-13 in de novo polyp formation

CRSwNP: Clinical and Observational Studies

- Prevalence of sleep disorders.
- Psychological impact CRSwNP
- Burden of Disease prevalence of type-2 inflammation in CRSwNP
- Development of additional patient tools to assess symptoms in CRSwNP
- Role-of surgery and burden of systemic steroids in patients with CRSwNP
- Underserved populations
- Unique sub populations of CRSwNP
- Comorbidities of high frequency in CRSwNP

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*****Any Preclinical Research Collaborations including:*

- *Proprietary animal models, cell lines, and/or other technologies.*
- *Approved medicines or therapeutic pipeline candidates for use in nonhuman studies.*
- *Can submit a research proposal at [Regeneron Preclinical Research Collaborations]*