SAFETY AND EFFICACY OF NOVEL MONOCLONAL ANTIBODIES FOR ENDOCRINE ORBITOPATHY

Sicherheit und Wirksamkeit neuer monoklonaler Antikörper zur Behandlung der endokrinen Orbitopathie

Dissertation

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Meiner Frau und Weggefährtin

PREFACE

This cumulative PhD thesis was performed in the academic clinical trial site of the Molecular Thyroid Research Laboratory (Lab Lead: Prof. Dr. med. George J. Kahaly), Department of Medicine I, Johannes Gutenberg-University (JGU) Medical Center, Mainz, Germany. The clinical trials and results were described in detail in the following published articles:

1) G. J. Kahaly, P. J. Dolman, **J. Wolf**, B. C. Giers, H. M. Elflein, A. P. Jain, et al. Proof-of-Concept and Randomized, Placebo-Controlled Trials of an FcRn Inhibitor, Batoclimab, for Thyroid Eye Disease. *J Clin Endocrinol Metab* 2023

2) **J. Wolf***, S. Alt*, I. Kramer, G. J. Kahaly. A Novel Monoclonal Antibody Degrades the Thyrotropin Receptor Autoantibodies in Graves Disease. *Endocr Pract* 2023
   * Equally contributed as first-authors

3) **J. Wolf**, I. Krämer, G. J. Kahaly. Safety and tolerability of anti-FcRn monoclonal antibody in thyroid autoimmunity. *Exploration of Immunology* 2024; 4(3): 341-357.

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1) J. Wolf, K. Lorenz, A. Othmann, A. Beck, H. M. Michel, et al. Secukinumab In Moderate-to-Severe Graves' Orbitopathy: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study. *J Clin Endocrinol Metab* 2025

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LIST OF ABBREVIATIONS

Abbreviation	Explanation
aAb	Autoantibodies
Ab	Antibody
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse events
AID	Autoimmune disease
AITD	Autoimmune thyroide disease
ALAT	Alanine aminotransferase
AP	Alkaline phosphatase
APC	Antigen-presenting cells
AS	Ankylosing spondylitis
ASAT	Aspartate aminotransferase
ATD	Thionamide antithyroid drugs
ATP	Adenosine triphosphate
Aza	Azathioprine
BC	B cells
CAS	Clinical activity score
CCL	C-C motif chemokine ligand
CDC	Complement-dependent cytotoxicity
COVID-19	Coronavirus disease 2019
CXCL	C-X-C motif chemokine ligand
CYP	Cytochrome-p450
CysA	Cyclosporine A
DON	Dysthyroid optic neuropathy
EO	Endocrine orbitopathy
EUGOGO	European Group on Graves' Orbitopathy
Fc	Crystallizable fragment
FcR	Crystallizable fragment receptor
FcRn	Neonatal crystallizable fragment receptor
FcγR	Fc-gamma receptors
GD	Graves' disease
GM-CSF	Granulocyte macrophage colony-stimulating factor
HDL	High density lipoprotein
HLA	Human leukocyte antigen
HT	Hashimoto's thyroiditis
IBD	Inflammatory bowel disease
IC	Immune complex
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IFN-γ	Interferon-gamma
Ig	Immunoglobulin
IGF-1R	Insulin like growth factor 1 receptor

Abbreviation	Explanation
IgG	Immunoglobulin G
IL	Interleukine
IL-21R	Interleukin 21 receptor
IL-23R	Interleukin 23 receptor
IVGC	Intravenous administered glucocorticoid
IVIG	Intravenous administered immunoglobulins
LDL	Low density lipoprotein
LN	Lupus nephritis
mAb	Monoclonal antibody
MedDRA	Medical dictionary for regulatory activities
MG	Myasthenia gravis
MHC	Major histocompatibility complex
MPA	Mycophenolic acid
mRNA	Messenger ribonucleic acid
MS	Multiple sclerosis
NK	Natural killer cells
NMOSD	Neuromyelitis optica spectrum disorder
OF	Orbital fibroblasts
OGC	Oral administered glucocorticoid
PPARγ	Peroxisome proliferator-activated receptor gamma
PsA	Psoriatic arthritis
PsO	Psoriasis
RA	Rheumatoid arthritis
RORγt	retinoid orphan receptor gamma t
SA	Serum albumin
SAE	Severe adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SE	Side Effect
SLE	Systemic lupus erythematosus
STAT3	Signal transducer and activator of transcription 3
SU	Subunit
TBAb	Blocking TSH-R-Ab
TC	T cells
TED	Thyroid eye disease
TGF-β	Transforming growth factor-beta
Th TC	T helper cells
Th17	IL-17 producing T cells
TNAb	Neutral TSH-R-Ab
TNF-α	Tumor necrosis factor-alpha
TPT	Teprotumumab
TRAb	TSH-R-Ab binding assay
Treg	Regulatory T cells
TSAb	Stimulating TSH-R-Ab

Abbreviation	Explanation
TSH-R	Thyrotropin receptor
TSH-R-Ab	TSH-R auto-antibodies
α-SU	Alpha subunit
β2m-SU	Beta-2-microglobulin subunit
γGT	γ-Glutamyltransferase

Summary

The endocrine orbitopathy (EO) represents the most common extrathyroidal manifestation of Graves' Disease (GD). In the course of the disease, inflammation-induced tissue remodelling of the orbital tissue occurs, which may progress to chronic alterations. The thyrotropin receptor (TSH-R) is the best-described autoantigen of EO. EO-specific TSH-R autoantibodies (TSH-R-Ab) cause an exceeding and uncontrolled activation of orbital target cells, leading to orbital inflammation. The pathogenesis of EO can be divided into an active, inflammatory, and inactive, chronic phase. Orbital tissue remodelling leads to impaired orbital function and often to psychosocial burden. In Europe only non-specific, immunosuppressive agents like glucocorticoids, mycophenolic acid, and Rituximab are available. These agents achieve beneficial improvements in various patients. However, the improvements are limited by side effects and are not permanent. The sole causal treatment option Teprotumumab is only available in the United States. There is a significant unmet medical need for novel and targeted treatment approaches.

The scope of this dissertation was to evaluate the safety and efficacy of two monoclonal antibodies in clinical trials, as potential, causal therapeutic options.

Batoclimab selectively inhibits the neonatal crystallizable fragment receptor (FcRn), which prolongs the half-life of immunoglobulins G (IgG). EO-specific TSH-R-Ab are of the IgG isotype. Therefore, inhibition of the FcRn is a promising novel approach. Results of the phase 2b clinical trial IMVT-1401-2001 demonstrated both, the safety and efficacy of the mAb in the treatment of patients with moderate-severe, active EO. Due to an unexpected increase in cholesterol and low-density lipoprotein cholesterol, the trial was terminated prematurely by the sponsor.

The pro-inflammatory cytokine interleukine-17 (IL-17) is associated with numerous autoimmune diseases. The potential use of Secukinumab, a selective IL-17 inhibiting mAb, for moderate-severe, active EO was evaluated in the phase 3 trial CAIN457ADE16 (ORBIT). A significant therapeutic effect compared to placebo could not be demonstrated. Nevertheless, a distinguished safety profile was observed. Due to the lack of efficacy, the trial was terminated prematurely by the sponsor.

Zusammenfassung

Die endokrine Orbitopathie (EO) stellt die häufigste extrathyreoidale Manifestation des Morbus Basedow dar. Im Krankheitsverlauf kommt es zu einer entzündlich bedingten Veränderung des orbitalen Gewebes, welche im weiteren Verlauf chronifizieren können. Das am besten charakterisierte Autoantigen der EO ist der Thyrotropinrezeptor (TSH-R). Durch TSH-R-spezifische Autoantikörper (TSH-R-Ak) wird eine unkontrollierte, übermäßige Aktivierung orbitaler Zielzellen induziert, welche zu den lokalen, chronischen Entzündungsreaktion führt. Die Pathogenese der EO lässt sich in zwei Phasen unterteilen: eine aktive, inflammatorische Phase und eine inaktive, chronische Phase. Die daraus resultierenden strukturellen Veränderungen des orbitalen Gewebes verursachen häufig Einschränkungen des Sehvermögens sowie erhebliche psychosoziale Belastungen. In Europa stehen derzeit ausschließlich unspezifisch, immunsuppressiv Substanzen wie Glukokortikoide (GC), Mycophenolsäure (MPS) oder Rituximab (RTX) zur Verfügung. Durch die verfügbaren Behandlungsoptionen lassen sich gute Erfolge bei vielen Patienten erzielen. Die Erfolge sind jedoch häufig durch Nebenwirkungen limitiert und nicht dauerhaft anhaltend. Die bislang einzige kausale Therapieoption, Teprotumumab, ist lediglich in den USA zugelassen. Der Bedarf an neuen, zielgerichteten Therapieansätzen zur Behandlung der EO ist groß.

Im Zuge dieser Dissertation wurde die Wirksamkeit und Sicherheit von zwei monoklonalen Antikörpern (mAb) als potenzielle, kausale Therapiemöglichkeiten im Zuge von klinischen Studien evaluiert.

Batoclimab hemmt selektiv den neonatalen Fc-Rezeptor (FcRn), der die Halbwertszeit von Immunglobulinen der Subklasse G (IgG) verlängert. Die EO spezifischen TSH-R-Ak gehören dem IgG-Typ an. Die Inhibition des stellt FcRn eine vielversprechende therapeutische Zielstruktur für die Behandlung der EO dar. In der Phase-2-Studie IMVT-1401-2001 konnte die Wirksamkeit und Sicherheit von Batoclimab bei Patienten mit moderat-schwerer, aktiver EO demonstriert werden. Bedingt durch einen unerwarteten Anstieg von Gesamt- und Low Density Lipoprotein (LDL) Cholesterin wurde die Studie vorzeitig durch den Sponsor beendet.

Das proinflammatorische Zytokin Interleukin-17 (IL-17) wird mit einer Vielzahl an Autoimmunerkrankungen assoziiert. Der potenzielle Einsatz von Secukinumab, einem anti-IL-17 mAb, bei Patienten mit moderater-schwerer, aktiver EO wurde in der Phase 3 Studie CAIN457ADE16 (ORBIT) evaluiert. Ein signifikanter Therapieeffekt im Vergleich zu Placebo konnte nicht nachgewiesen werden. Im Verlauf der Studie zeigte sich ein ausgezeichnetes Sicherheitsprofil von Secukinumab, das mit bisherigen Publikationen im Einklang steht. Aufgrund der ausbleibenden Wirksamkeit wurde die Studie ebenfalls vorzeitig beendet.

1 INTRODUCTION

1.1 Autoimmune diseases

Autoimmune diseases (AID) are characterized by the loss of body tolerance to its own structures (self-tolerance). The immune system is unable to distinguish between self and foreign structures. As a result, the body's immune defense system targets its own tissues (1, 2). The prevalence of AID approximates 5% in the general population. Women have a 10-fold higher likelihood of developing an AID than men (1-4). The maintenance of self-tolerance is physiologically ensured through central (elimination of autoreactive cells during the maturation process) and peripheral (inactivation or lack of activation of autoreactive immune cells) mechanisms.

Central mechanisms include the positive and negative selection of T cells (TC) and B cells (BC) during maturation. During this process, maturing immune cells are exposed to self-antigens. If a maturing lymphocyte exhibits an excessive reaction to a self-antigen, it is eliminated through apoptosis. This mechanism reduces the number of autoreactive immune cells that reach the periphery (2, 5, 6). In the periphery, additional mechanisms prevent the development of AIDs as follows: (A) clonal deletion (direct inactivation of lymphocytes by inhibitory ligands), (B) clonal anergy (lack of expression of necessary co-stimulatory molecules in tissues), (C) ignorance (physical separation of possible antigens from lymphocytes), and (D) suppression of lymphocytes by regulatory T cells (Treg). Despite these strict control mechanisms, autoreactive lymphocytes can reach the periphery, potentially leading to loss of self-tolerance (5, 7, 8). However, presence of autoreactive TC and BC does not necessarily indicate an AID as autoreactive lymphocytes can be detected in healthy individuals without AID.

Loss of self-tolerance is a multifactorial process influenced by both endogenous and exogenous factors. Endogenous (non-modifiable) factors include genetic predispositions and gender (1, 9, 10). The literature describes a variety of genes that potentially influence the development of an AID, the most studied being human leukocyte antigen (HLA) I and HLA II genes. A positive family history of AID increases the risk of developing AIDs. However, children with AIDs do not necessarily develop the same disease as their parents. Women have a 10-fold increased risk of developing AIDs compared with men (2, 3, 6, 9). Exogenous (modifiable) factors include lifestyle, e.g., diet, smoking habits, and molecular factors like infections. A high-salt diet can promote the formation of Interleukin (IL)17-producing T helper cells (Th17), which are associated with several AIDs. Both malnutrition and overnutrition can contribute to the development of an AID. Smoking is generally associated with onset and progression of various AIDs. Infections, particularly severe or prolonged ones, can cause tissue damage, leading to the release of intracellular autoantigen (antigen demasking). Furthermore, pathogenic antigens can interact with self-structures (cross-reactivity) or share structural homologies with self-structures (molecular mimicry), resulting in immune cell sensitization and initiation of an autoimmune response (1-3, 6, 11).

The immune system targets the body's own structures subsequent to loss of self-tolerance. Immune response is mediated by either autoreactive effector cells or autoreactive antibodies (aAb). During an AID, there is often a switch in antigens, as chronic inflammation leads to tissue damage and the release of new autoantigens (epitope spreading) (1, 2, 11).

AID can be classified according to the type of effector mechanism: (A) cell-mediated and (B) aAb-mediated AID (9, 12). There are also hybrid forms in which both cellular and antibody-mediated mechanisms are involved. Furthermore, AID can be categorized as (A) organ-specific or (B) systemic (2, 3, 9). Examples of systemic AID include Sjögren's syndrome, rheumatoid arthritis (RA), and systemic lupus erythematosus (SLE), which affect multiple organs or the entire body. Organ-specific AIDs, such as Graves' disease (GD), Hashimoto's thyroiditis (HT), and myasthenia gravis (MG), are generally restricted to specific organs.

Auto-Ab can be detected in the serum years before the clinical onset of AID. However, presence of aAb does not necessarily lead to AID development. Auto-Ab can also be found in the serum of healthy individuals. Auto-Ab are highly specific for a particular AID, while multiple aAb can be present in a few diseases, e.g., MG. Due to their high specificity and early detectability, immunoglobulins (Ig) are valuable for diagnosis of AID, and prediction of both disease progression and therapy response (6, 13-17).

1.2 Endocrine orbitopathy

1.2.1 General information

Endocrine orbitopathy (EO), also referred to as thyroid eye disease (TED), is an organ-specific AID and represents the most common extrathyroidal manifestation of GD (18-22). Clinically, 50–60% of patients with GD develop EOwithin 18 months following diagnosis (23-25). EO occurs prior or or after GD onset. EO also occurs in patients with HT or in euthyroid patients without thyroid pathology. However, approximately 90% of EO patients exhibit hyperthyroidism in clinical practice (19, 26-28). The estimated prevalence ranges from 90 to 300 per 100,000 individuals, with sex-dependent incidence rates of 0.9–2.9 and 3.3–16.7 per 100,000 per year for men and women, respectively (19, 29-31).

1.2.2 Clinical apperance

Clinical signs and symptoms of include ocular irritation, increased tearing, photophobia, and ocular pain during the early phase of the disease. As condition progresses, patients may experience impaired ocular motility, proptosis, and diplopia, which significantly reduce quality of life. Severe cases may result in visual impairment, including complete vision loss (22, 32-34).

EO is a biphasic AID characterized by an active inflammatory and a chronic inactive phase. Rundel et al. initially described the disease course of EO (Figure 1) (35, 36). During the active phase, localized inflammation occurs in the orbital tissues. Key clinical features include: (A) redness and swelling of the eyelids, (B) conjunctival redness and swelling, and (C) swelling of the plica or caruncle (32, 37, 38).

These clinical signs along with the presence of spontaneous and movement-dependent pain are used to assess disease activity using the clinical activity score (CAS). Each symptom is assigned a value of 1 if present, resulting in a maximum score of 7. A CAS of ≥3/7 confirms active EO. In the chronic phase, active inflammation subsides, and tissue remodeling with fibrosis definitely changes orbital tissue. In addition to clinical activity, the severity of TED is evaluated using the 'NO SPECS' classification. Based on disease activity and severity, professional medical societies provide treatment recommendations (32, 37-41).

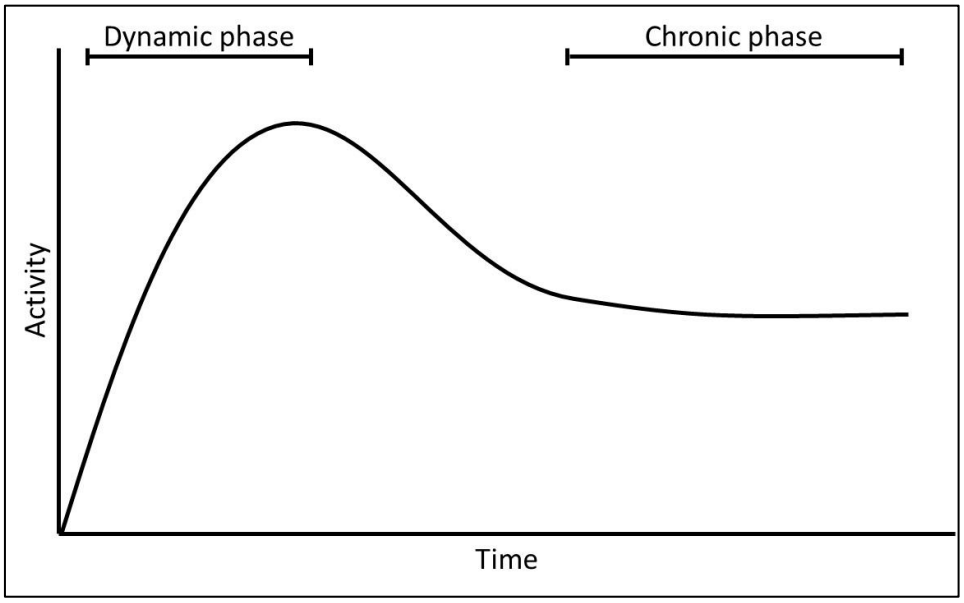

Figure 1 Progression of endocrine orbitopathy (modified Rundle's curve) (35, 36)

1.2.3 Risk factors

Endogenous and exogenous risk factors for EO manifestation are summarized in Table 1. Women develop 2-3-fold more often EO than males, whereas men often exhibit more severe forms. The most significant and modifiable risk factors are: (A) smoking, (B) thyroid dysfunction, and (C) high titers of thyrotropin receptor (TSH-R) auto-antibodies (TSH-R-Ab). Smokers have a four-fold increased risk of developing EO and show delayed and reduced response to therapy. The negative effects are correlated with the number of cigarettes consumed. Patients with thyroid dysfunction (hyper- or hypothyroidism) experience more severe clinical courses. Finally, a high concentration of stimulating TSH-R-Ab (TSAb) is an additional negative predictive factor.

Table 1: Endo- and exogenous risk factors

Exogenous risk factors (non-modifiable factors)	
Age	(30, 31, 42, 43)
Anatomic/morphological variants	(24, 44)
Genetics	(21, 30, 43-46)
(Race and ethnicity)	(21, 30, 31, 47)
Sex	(21, 25, 30, 31, 43, 46, 47)
Endogenous risk factors (modifiable factors)	
Hypercholesterinemia	(30, 48, 49)
GD specific treatment (radioactive iodine administration)	(21, 30, 43, 44, 47, 50)
Smoking	(21, 22, 30, 33, 42-44, 46, 47, 51)
TSH-R-Ab	(30, 31, 43, 47, 52)
Thyroid biochemical function	(30, 31, 43, 44, 47, 53-56)

GD= Graves' disease, TSH-R-Ab= Thyrotropin receptor auto-antibodies. Potential risk factors are shown in brackets.

1.2.4 Treatment options for endocrine orbitopathy

Current therapeutic options primarily focus on symptomatic treatment using nonspecific immunosuppressive and anti-inflammatory agents. However, efficacy of these interventions is restricted to the active inflammatory phase of the disease, while their efficacy is rather poor during the chronic phase (55, 57-60). In accordance with the current guidelines of the European Group on Graves' Orbitopathy (EUGOGO), the management of EO should rely on both disease activity and clinical severity (mild, moderate-severe, sight-threatening). Treatment should be provided in specialized centers rather than in general practice to ensure optimal patient care (55, 58, 61).

Regardless of disease severity, all patients should (A) receive supportive symptomatic therapy with lubricating/moisturizing eye drops, (B) achieve biochemical euthyroidism, (C) abstain from or significantly reduce nicotine consumption, and (D) ensure adequate control of serum cholesterol levels (48, 49, 55, 56, 58, 59, 62).

In patients with mild EO, aggressive pharmacological intervention is not indicated. As spontaneous remission occurs in approximately 60% of cases, a 'watchful waiting'

approach is considered appropriate. In addition, EUGOGO recommends daily supplementation with selenium for up to six months (56, 58, 59, 63).

Patients with moderate-severe EO comprise the primary target group for pharmacological intervention. The goal of treatment is to shorten the active inflammatory phase and the remodeling of the orbital tissue. According to the EUGOGO guidelines, first-line therapy consists of high-dose intravenous glucocorticoids (IVGC), along with mycophenolic acid (MPA), as this combination has demonstrated superior efficacy compared with monotherapies (55, 57, 58, 62). However, 20–30% of patients show an inadequate therapeutic response or experience relapse following treatment cessation (55, 56, 58, 64, 65). Second-line therapeutic options include (A) a second cycle of high-dose IVGC, (B) oral glucocorticoids (OGC) combined with immunosuppressants such as azathioprine (Aza) or cyclosporine A (CysA), (C) targeted orbital radiotherapy, (D) the anti-CD20 monoclonal antibody (mAb) Rituximab, (E) the anti-IL-6 mAb Tocilizumab, or (F) the insulin like growth factor 1 receptor (IGF-1R) inhibiting mAb Teprotumumab (TPT) (55, 56, 58, 64, 66). An overview of the recommended treatment options for moderate-severe EO is provided in figure 2.

For sight-threatening EO, very high-doses of IVGC administered every second day or emergency orbital decompression are recommended.

1.2.4.1 Limitations of Current Therapeutic Options

With the exception of TPT, currently available treatment strategies rely on nonspecific immunosuppressive agents that do not directly target the underlying pathophysiological mechanisms of TED. This lack of specificity is associated with a high risk of adverse events. For example, IVGC is contraindicated in patients with severe unstable diabetes mellitus, severe hepatic disease, or uncontrolled hypertension. Furthermore, the cumulative IVGC dose is limited to a maximum of 8 g per cycle, because higher cumulative doses, significantly elevate the risk of adverse events (AE). Although TPT is a receptor-targeted therapy, it is also associated with relevant side effects. Clinical studies have reported an increased incidence of hearing impairment, hyperglycemia, and dermatological complications.

The adverse events associated with nonspecific treatment strategies were comprehensively characterized and discussed in the work of Wolf et al. (67). Given these limitations, there remains a substantial clinical need for innovative, targeted, and better-tolerated therapeutic options, which are currently the focus of extensive clinical research.

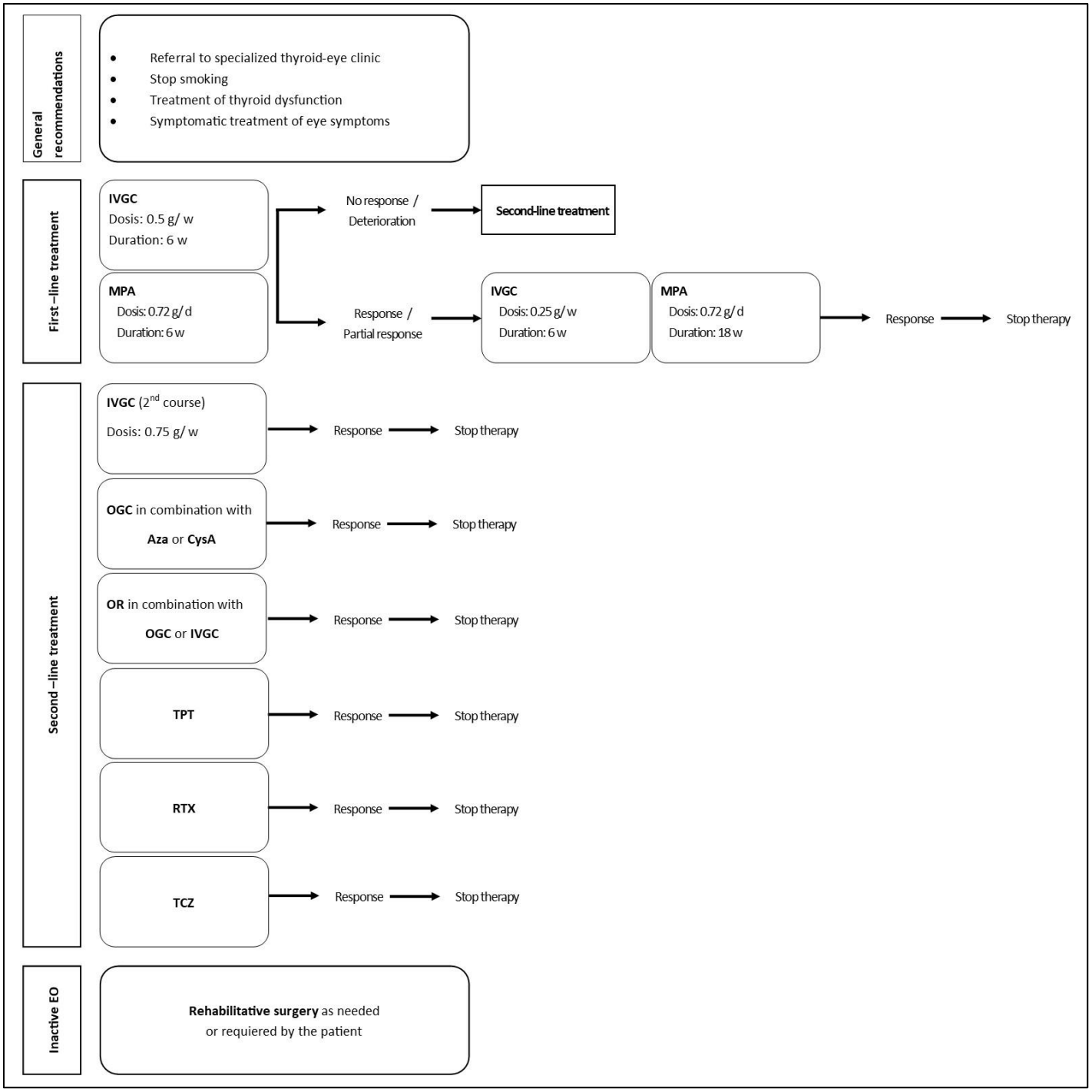

Figure 2 Recommended treatment options for moderate-severe endocrine orbitopathy

Aza= Azathioprine, CysA= Cyclosporine A, EO= Endocrine orbitopathy, IVGC= Intravenous glucocorticoids, MPA= Mycophenolic acid, OGC= Oral glucocorticoids, OR= Orbital radiation, RTX= Rituximab, TCZ= Tocilizumab, TPT= Teprotumumab

1.3 The neonatal crystallizable fragment receptor

1.3.1 Structure and distribution

The neonatal crystallizable fragment (Fc) receptor (FcRn) is a membrane-bound receptor belonging to the Fc receptor (FcR) family. Although included in the FcR familiy, FcRn differs significantly in both structure and function from other members of this family. Structurally, FcRn resembles major histocompatibility complex (MHC) receptors more closely (68-71). It is composed of two non-covalently linked subunits (SU): a heavy, insoluble alpha subunit (α-SU) and a light, soluble beta-2-microglobulin subunit (β2m-SU). The α-SU comprises three α helix motifs, a transmembrane anchor, and an intracellular tail, which is critical for proper receptor function. While the β2m-SU is essential for proper protein folding (figure 3, panel A) (71-73). Notably the α-SU harbors a characteristic MHC-like groove that is sterically blocked, preventing FcRn from presenting antigens, unlike MHC molecules (70, 72, 74, 75).

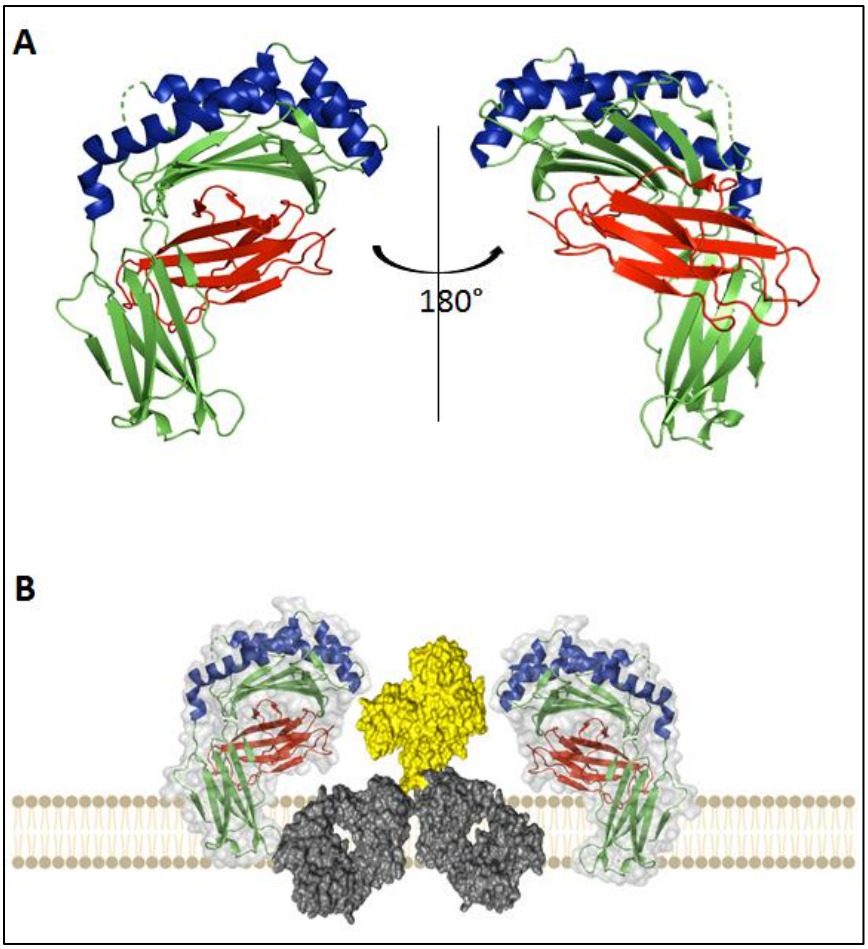

Figure 3: Crystal structure of the neonatal crystallizable fragment receptor and interaction with its ligand immunoglobulin G

Panel A: Crystallographic structure of the neonatal crystallization fragment receptor (FcRn). The alpha subunit displayed in green, and the beta subunit displayed in red color. Within the alpha subunit, the three relevant α helices (α1-α3) for the interaction with immunoglobulin g (IgG) highlighted with blue color. **Panel B:** The FcRn interacts with its ligand IgG in an 2:1 (FcRn:IgG) stoichiometry. Relevant amino acids for the interaction are located at the α helices and β2m subunit and the crystallization fragment (highlighted in yellow) of the FcRn and IgG, respectively. (PDB ID: 1EXU, 1IGY)

Initially identified in the intestinal epithelium of rodents and human placental tissue, FcRn is ubiquitously expressed throughout the body (see table 2). FcRn expression is most pronounced in epithelial and endothelial cells, as well as hematopoietic cells, which play significant roles in blood filtration and circulation. However, FcRn is not expressed in natural killer cells (NK), BC, or TC. Its expression is predominantly intracellular, localized in early endosomes, with minimal presence on the cell surface (74-79).

Table 2: Expression of the neonatal crystallizable fragment receptor

Tissue or organ expressing the FcRn	
Blood vessels	(77, 80-83)
Brain / Blood-brain-barrier	(78, 84, 85)
Eye	(86-88)
Haemopoietic cells	(89-93)
Intestinal	(82, 90, 94-96)
Kidney	(90, 97)
Liver (Hepatocytes)	(78, 84, 90, 98-100)
Lung	(53, 85, 90, 99, 101-103)
Placenta	(79, 82, 104-106)
Skeletal muscle and skin	(90)
Spleen	(90, 99)
Thyrocytes	(107)
Tissue or organ not expressing the FcRn	
BC, TC, NK cells	(89, 90, 99, 108)

BC= B-cells, FcRn= neonatal crystallizable fragment receptor, NK cells= natural killer cells, TC= T-cells

1.3.2 Ligand interaction and mechanism of action

FcRn's primary ligands are IgG and serum albumin (SA). Under physiological conditions, its functions include (A) transcytosis of ligands across cellular barriers, (B) extending ligand half-life through recycling mechanisms, and (C) assisting phagocytosis of antigen-IgG complexes in the gut and antigenpresentation (74, 76, 81, 109). In adults, FcRn facilitates the bidirectional transport of IgG and immune complexes, whereas it plays a crucial role in fetal or neonatal immunity by mediating the maternal IgG transfer, initiating the immune defense system.

FcRn binds IgG and SA simultaneously without interference, utilizing distinct and spatially separate binding sites (77, 78, 83, 110). The stoichiometry of FcRn-IgG interaction is 2:1 (figure 3, panel B), while FcRn-SA interaction exhibits a 1:1 ratio (68, 69, 74, 75). Independent of ligand type or mechanism of action, the FcRn processes involve three main steps: (I) Ligands are internalized via pinocytosis into early endosomes, where FcRn is expressed. (II) Endosomal acidification via adenosine triphosphate (ATP)-dependent proton pumps facilitates FcRn-ligand binding through histidine protonation. (III) Bound ligands are spared lysosomal degradation and returned to the cell surface via vesicles. At the neutral extracellular pH, the histidine deprotonation leads to ligand-receptor dissociation. These strict pH-dependent mechanisms are highly selective, enabling FcRn to bind all IgG subtypes but no other immunoglobulins or serum proteins (78, 83, 84, 95, 99). As a functional illustration, the recycling mechanism of IgG is exemplified in figure 4.

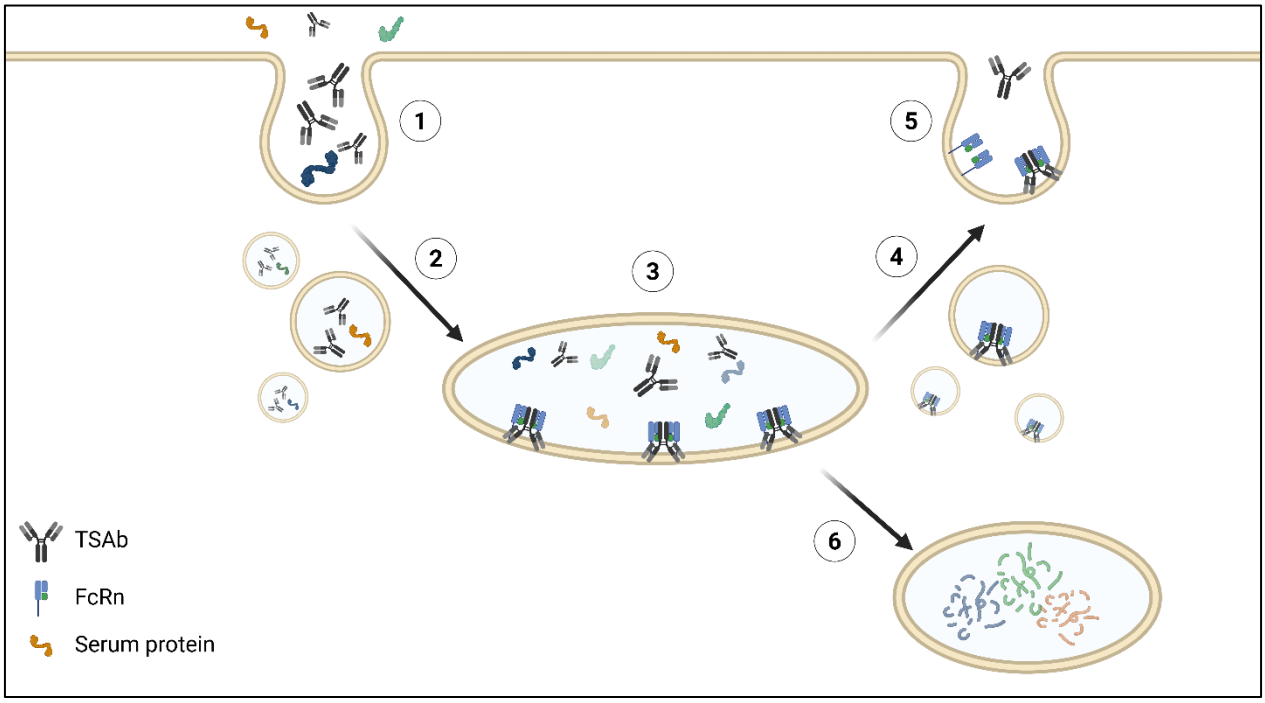

Figure 4: Recycling mechanism of the crystallization fragment receptor
FcRn= Neonatal crystallization fragment receptor, TSAb= Thyrotropin receptor stimulating auto-antibody

Serum proteins and TSAb are taken up into the cell via spontaneous pinocytosis (**1**) and transported into early endosomes (**2**). Following endosomal acidification, TSAb can bind to FcRn in a pH-dependent manner (**3**). Bound TSAb are then transported back to the cell surface in vesicles (**4**). In the neutral to slightly basic pH of the peripheral bloodstream, the TSAb-FcRn complex dissociates spontaneously (**5**). Unbound serum proteins and/or immunoglobulins are subsequently degraded in lysosomes (6).

1.3.3 FcRn as potential target for autoimmune diseases

FcRn does not distinguish between physiological and pathological IgG. In IgG-mediated AID, the recycling mechanism of FcRn can amplify disease progression by increasing the half-life of aAb. FcRn also explains the maternal-to-fetal transfer of IgG-mediated AID (104, 111, 112).

Animal models have demonstrated that β2m-SU deficiency results in (A) accelerated IgG catabolism, reducing its half-life from approximately 21 to 6–7 days, (B) significantly lower serum IgG levels, and (C) increased resistance to IgG-mediated AID development (85, 113-119). However, beside the FcRn impairment, β2m-SU deficiency also impairs MHC molecule formation, indicating its dual necessity for MHC and FcRn functionality.

This comprehensive understanding of FcRn provides insights into its pivotal role in immunological processes and its therapeutic potential in treating AID. Potential strategies include (A) conjugating macromolecular drugs with Fc fragments for enhanced epithelial absorption (74, 77, 120), (B) modifying Fc fragments of therapeutic mAb to modify their half-life (77, 114, 121), and (C) inhibiting FcRn to degrade pathogenic aAb in IgG-mediated AID (101-103). Emerging anti-FcRn therapeutics are under clinical evaluation for treating AID such as MG, pemphigus, and primary autoimmune thrombocytopenia (122-131).

Immunohistochemical analyses of orbital tissue show significant overexpression of the TSH-R in patients with EO (132-134). TSH-R is expressed by orbital fibroblasts (OF) and fibrocytes as precursor cells (22, 135-137). OF serve as both target and effector cells in EO. Stimulation of the TSH-R by TSH-R-Ab induces the secretion of cytokines and chemokines and promotes the differentiation of OF into adipocytes and myofibroblasts. Auto-antibodies targeting TSH-R are key biomarkers for EO (132, 138). Animal models have shown that TSH-R-Ab transfer can trigger both experimental hyperthyroidism and EO.

TSH-R-Ab can be functionally categorized as TSAb, blocking (TBAb), or neutral Ab (TNAb) (139-143). In GD and EO, TSAb are of particular importance because they are polyclonal IgG-antibodies (Ab) that cause excessive activation of Gs-coupled TSH-R. This activation is not subject to the negative feedback mechanisms observed in physiological thyrotropin stimulation. Consequently, this leads to unregulated thyroid hormone synthesis, proliferation, and enhanced survival of thyrocytes and OF (132, 141, 144, 145). TSAb are therefore pivotal to both the onset and persistence of disease (146, 147).

TSH-R-Ab are detectable in the serum of 90% of patients with EO, with titer levels correlating with clinical disease severity and activity (132, 133, 138, 144, 148). Patients with severe, vision-threatening EO exhibit the highest serum TSAb concentrations. Quantifying TSH-R-Ab is crucial for predicting disease course and evaluating therapeutic outcomes. Persistently high TSH-R-Ab titers during antithyroid and/or immunosuppressive therapy are often associated with reduced therapeutic efficacy and an increased risk of relapse (47, 138, 143, 148-151). Compared with conventional TSH-R-Ab measurement (TRAb), TSAb measurement via cell-based bioassays offers greater sensitivity and precision in assessing the clinical manifestations and progression of EO.

Due to the IgG phenotype of TSH-R-Ab and their critical role in EO manifestation and maintenance, FcRn is a promising therapeutic target. FcRn does not distinguish between

physiological and pathological IgG, thereby extending the half-life of IgG, including pathogenic TSH-R-Ab.

Besides prolonging the half-life of IgG and IgG-like TSH-R-Ab, the FcRn plays a role in antigen presentation. IgG-antigen immune complexes (IC) are absorbed by antigen-presenting cells (APC) via FcR (especially Fc-gamma receptors, FcγR) (78, 91, 152, 153). After absorption antigens are degraded and presented on MHC I and II molecules. Antigen presentation is enhanced by endosomal FcRn through crosstalk with FcγR. Furthermore, FcRn mediates an antigen cross-presentation, admitting a presentation on both MHC molecules. Despite the activation of immune cells of the specific immune system, FcRn can directly cause cytokine synthesis of innate immune cells like macrophages and monocytes. The complementary receptor interaction is augmented further under acid or inflammatory conditions (152).

Batoclimab (RVT-1401) is a fully human mAb of the IgG1 subclass that specifically inhibits FcRn. It exhibits higher affinity for FcRn under both acidic and neutral pH conditions than native IgG molecules. Additionally, the Fc region of Batoclimab was biochemically engineered to minimize effector functions like complement-dependent cytotoxicity (CDC) and antibody-dependent cellular cytotoxicity (ADCC), thereby reducing potential adverse effects. Preclinical and animal studies have shown that Batoclimab reduces systemic IgG levels by 60-80% in preclinical studies, depending on the dose and frequency of administration. This effect was transient since IgG levels spontaneously normalize after treatment discontinuation. Notably, no significant effects on other Ig classes (e.g., IgA or IgM) were observed (154).

Batoclimab was investigated in the ASCEND GO 2 (RVT-1401-2001) study, a placebo-controlled, double-blind, multicenter Phase 2 trial. In this study the safety, efficacy, and tolerability of Batoclimab was evaluate in patients with active, moderate-to-severe EO.

1.4 IL-17 and Th17 cells

T lymphocytes are essential immune cells that play central roles in both innate and adaptive immune systems. They are classified based on their surface markers into CD4+ and CD8+ TC. CD4+ T helper cells (Th TC) are distinguished according to their cytokine profile. Originally, two main subtypes were described: Th1 and Th2 cells, which primarily produce interferon-gamma (IFN-γ) and IL-4, respectively (155-158). This paradigm has been expanded to include additional subgroups. A relatively newly described type of Th TC is the Th17 subset, which primarily produces IL-17 (159-161).

Th17 TC express various pro-inflammatory cytokines in addition to IL-17, including IL-6, IL-22, IL-21, IL-23, and granulocyte macrophage colony-stimulating factor (GM-CSF) (162-165). Differentiation is promoted by IL-6 along with transforming growth factor-beta (TGF-β) and IL-22, leading to enhanced proliferation in the inflammatory microenvironment. Cytokines secreted by Th17 cells inhibit the proliferation of Th1 and Th2 TC, whereas IFN-γ and IL-4, in turn, suppress Th17 TC proliferation (159, 162, 166, 167). To date, no autocrine-positive feedback loop of IL-17 on Th17 TC proliferation has been demonstrated. IL-23 does not directly affect proliferation but significantly extends the lifespan of these cells, thereby indirectly influencing their differentiation. Under physiological conditions, Th17 TC are involved in immune defence against fungi and exogenous bacteria. Mouse models of IL-17 deficiency show increased susceptibility to

infections (159, 168, 169). The IL-17 cytokine family consists of six members (A-F), which can form homo- or heterodimers. IL-17A/A, IL-17A/F, and IL-17F/F (hereafter referred to as IL-17) are particularly implicated in AID. IL-17 binding to its receptor activates intracellular signalling pathways that lead to (A) the induction of proinflammatory genes and (B) increased stability of transcribed messenger ribonucleic acid (mRNA) (162, 166, 170, 171).

IL-17 is often described as a ‘fine-tuning factor’ of immune responses, as its effect is enhanced by cytokines such as IFN-γ, IL-1β, and tumor necrosis factor-alpha (TNF-α). In addition to their physiological function, Th17 TC contribute to chronic inflammation (162, 170, 172-174). Elevated Th17 cell numbers have been observed in patients with AID, including RA, psoriasis, multiple sclerosis (MS), and asthma (159, 162). Most Th17 cells are CD45RO+ memory T cells, suggesting antigen sensitization with autoantigen. Recent studies have indicated that a pathogenic subset of Th17 cells capable of producing IFN-γ (Th17.1 phenotype) can also be detected in patients with AID (175-177).

Patients with EO exhibit increased immune cell infiltration in orbital tissue, with CD3+ TC representing the dominant cell population. Both CD4+ and CD8+ T cells are detectable, predominantly as CD45RO+ memory T cells. The literature provides conflicting data on the Th1-to-Th2 TC-ratio in orbital tissue. Recent findings suggest a shift during the disease course, with Th1 being more prevalent in the early and Th2 cells predominating in the chronic phase. During the active phase, immune cell infiltration in orbital tissue is significantly increased, suggesting a role for chronic inflammation in disease pathogenesis (21, 22, 175, 178, 179). The infiltrating immune cells contribute to (A) enhanced activation of BC and aAb production, (B) stimulation of OF proliferation and differentiation, (C) upregulation of adhesion molecules, MHC-II, and CD40, and (D) increased secretion of pro-inflammatory cytokines (IL-6, IL-16, IL-23, TNF-α) and chemokines (C-X-C motif chemokine ligand (CXCL) 9, CXCL10, C-C motif chemokine ligand (CCL) 2, CCL5) (155, 177, 180-185).

Elevated Th17 cell numbers have been detected in the orbital tissue, serum, and tear fluid of EO patients (176, 180-184). These cells exhibit altered expression patterns, including increased IL-23 receptor (IL-23R) expression and decreased IL-21 receptor (IL-21R) expression. The IL-23R-mediated effect extends Th17 cell lifespan, whereas reduced IL-21R expression impairs the immune suppression of these cells. A high proportion of Th17 cells in patients with EO belongs to the pathogenic Th17.1 subset (producing both IL-17 and IFN-γ). In patients who are resistant to steroid treatment, the number of Th17.1 TC is significantly elevated (57, 175, 176, 184). Clinically, the Th17 TC count was positively correlated with both TED disease activity and severity. An increased IL-17 titer has been detected in serum, tear fluid, and orbital tissue, showing a positive correlation with TED activity and severity (175, 179, 180, 182). However, contradictory findings exist regarding the correlation between IL-17 levels and TSH-R-Ab titers (186, 187).

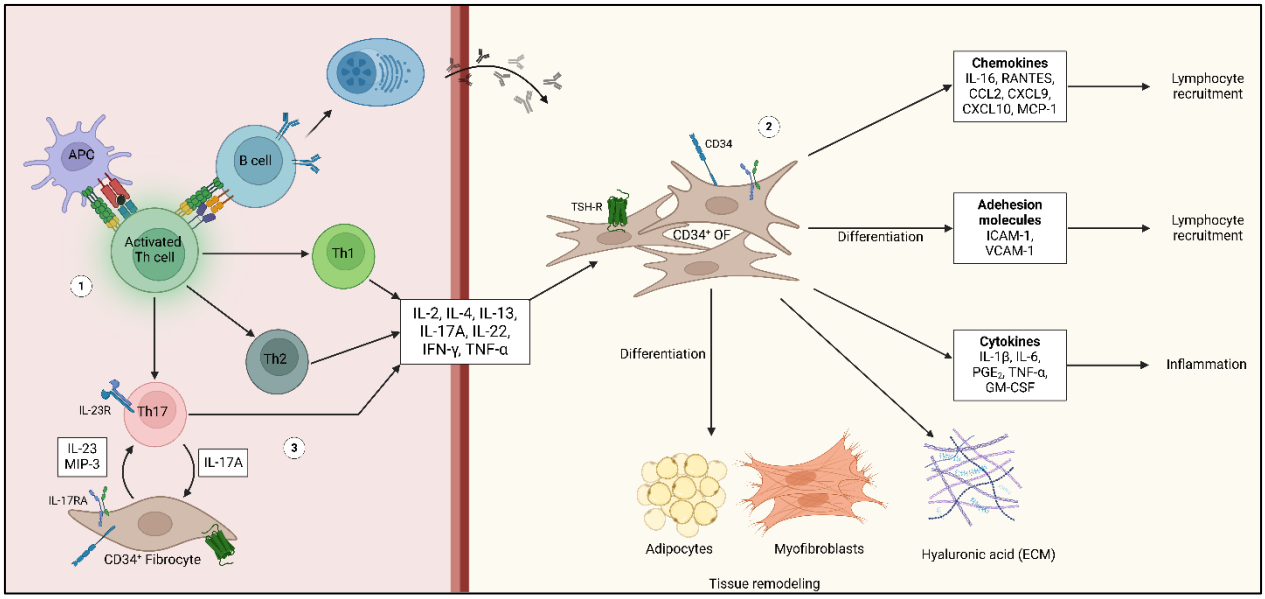

Figure 5: Inflammatory process and the mechanism of IL-17 in endocrine orbitopathy pathogenesis (modified from (184))

① During the manifestation of endocrine orbitopathy (EO), increased infiltration of immune cells including T cells (TC), B cells (BC) and monocytes into orbital tissue is observed. Presentation of autoantigen fragments by antigen-presenting cells (APCs) triggers the activation of T helper cells (Th TC). Activated Th cells can subsequently activate BC and promote their differentiation into plasma cells. Plasma cells secrete autoantibodies targeting the structure of the presented autoantigens. Depending on the stimulus, activated Th TC can differentiate predominantly into Th1, Th2, or Th17 subsets. ② Autoantibodies against the TSH receptor (TSH-R), along with cytokines secreted by Th TC, lead to the activation of CD34+ orbital fibroblasts (OF). Activated OF differentiate either into adipocytes or myofibroblasts, and secrete glycosaminoglycans (GAG) such as hyaluronic acid. This leads to an increased volume of the orbital tissue and morphological changes. Activated OF secrete pro-inflammatory cytokines, chemokines and have an increased expression of adhesion molecules. The enhanced expression of chemokines and adhesion molecules facilitates the further infiltration of immune cells into the orbital tissue. ③ The Th17 TC subset primarily secrete the pro-inflammatory interleukins (IL) IL-17 and further pro-inflammatory mediators like IL-6 and tumor necrosis factor-alpha (TNF-α). IL-17 orchestrates inflammatory processes. IL-17 activates and stimulates CD34+ fibrocytes and OF. Activated fibrocytes, similar to OF, can secrete pro-inflammatory mediators. The cytokines secreted by fibrocytes and OF enhance Th17 cell proliferation and survival, thereby sustaining and amplifying the inflammatory response. Consequently, the IL-17/IL-23 axis is a critical factor in maintaining and worsening chronic inflammation in TED.

1.4.1 IL-17 as a potential target for endocrine orbitopathy

In mouse models, IL-17 deficiency leads to delayed onset or milder forms of AID. Inhibition of the IL-17 axis in long-standing AID models has resulted in clinical improvement and, in some cases, remission without general suppression of TC immunity (159, 160, 188, 189). Secukinumab (AIN457) is a human IgG1 mAb that selectively binds IL-17A and promotes its elimination, thereby reducing its pro-inflammatory effects. Secukinumab has already been approved for the treatment of plaque psoriasis in children and adults, hidradenitis suppurativa (acne inversa), psoriatic arthritis, and juvenile psoriatic arthritis (190). However, its use in TED has not yet been investigated. The multicenter, double-blind, randomized, placebo-controlled Phase 3 trial CAIN457ADE16 (ORBIT) is the first to evaluate Secukinumab for treating active moderate-severe EO.

1.5 Aim of the PhD Thesis

Patients with EO not only suffer from visible changes and functional impairments of the eyes but also often experience a significant impairment in their quality of life, which frequently leads to social withdrawal. Medical and social needs for effective therapies are therefore high. Currently, no causal therapies are available in Europe. The mAb TPT, which has been approved only in the United States, represents the sole causal therapeutic option at the moment. EUGOGO recommends immunosuppressive agents, such as glucocorticoids, MPA, and mAb like Tocilizumab and Rituximab, for the treatment of EO. Approximately 70% of treated patients show a positive treatment response. However, due to their non-specific and nonselective mechanisms of action, AE are common. This highlights the urgent need for new, targeted therapeutic approaches.

The aim of this PhD thesis was to evaluate the efficacy and safety of two mAb: Batoclimab (targeting the FcRn), and Secukinumab (targeting IL-17A), for the treatment of EO. Batoclimab inhibits the recycling mechanism of TSH-R-Ab, resulting in an increase catabolism of the aAb. Secukinumab directly inhibits the pro-inflammatory fine-tuning cytokine IL-17A. The target structures of these mAb play a crucial role in the pathogenesis and maintenance of EO and thus represent potentially new approaches for a causal therapy.

2 RESULTS

2.1 Publication of the clinical trial IMVT-1401-2001

2.1.1 Proof-of-concept and Randomized, Placebo-controlled Trials of an FcRn Inhibitor, Batoclimab, for Thyroid Eye Disease

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Summary:
The manuscript presents data from the Phase 2a, Proof-of-Concept study (IMVT-1401-1002) and the randomized, placebo-controlled, multicenter, double-blind Phase 2b study (IMVT-1401-2001). In the Phase 2a study, treatment with the mAb Batoclimab significantly reduced total IgG and IgG subclasses. Additionally, a marked reduction in EO-specific aAb (TRAb and TSAb) was observed. Regarding the primary endpoint, 3 out of 7 treated patients demonstrated improvement in CAS, proptosis, or diplopia. The promising results from this early Phase 2a study served as the rationale for initiating the Phase 2b study.

In the IMVT-1401-2001 trial, three different doses of Batoclimab were compared with placebo. In the active treatment groups, therapy resulted in a dose-dependent, reversible reduction in the IgG and IgG subclasses. Furthermore, significant suppression of TRAb and TSAb was observed. Although there was no statistically significant difference in the primary endpoint between the treatment and placebo groups, differences in proptosis, diplopia, and CAS were noted at earlier time points. Suggesting that Batoclimab may have a relevant effect on proptosis and orbital tissue volume. The therapy was generally well tolerated. The most frequently reported AE were injection site reactions, fatigue, dizziness, and nausea. Three severe AE (SAE) occurred during the trial (two in the treatment groups and one in the placebo group), none of which were deemed treatment-related. A dose-dependent reduction in serum albumin levels was observed in the treatment groups, which spontaneously normalized during the follow-up period. Phase 2b study was prematurely terminated because of an unexpected increase in cholesterol levels (total cholesterol and low density lipoprotein, LDL). The increase in cholesterol levels was positively correlated with the decline in serum albumin levels and spontaneously normalized during the follow-up period.

Both studies demonstrated the efficacy of Batoclimab through the reduction of IgG, EO-specific aAb, and improvement of clinical signs and symptoms. The therapy was well tolerated, no patients discontinued the study due to AE. Additionally, in the Phase 2b study, Batoclimab treatment was associated with normalization of thyroid function, suggesting that Batoclimab may also represent a potential therapeutic option for GD.

Contributions:

- Study coordination and organization
- Drafting the manuscript
- Interpretation of results
- Critical evaluation and revision

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Clinical Research Article

Proof-of-concept and Randomized, Placebo-controlled Trials of an FcRn Inhibitor, Batoclimab, for Thyroid Eye Disease

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Abstract

Context: Inhibition of the neonatal fragment crystallizable receptor (FcRn) reduces pathogenic thyrotropin receptor antibodies (TSH-R-Ab) that drive pathology in thyroid eye disease (TED).

Objective: We report the first clinical studies of an FcRn inhibitor, batoclimab, in TED.

Design: Proof-of-concept (POC) and randomized, double-blind placebo-controlled trials.

Setting: Multicenter.

Participants: Patients with moderate-to-severe, active TED.

Intervention: In the POC trial, patients received weekly subcutaneous injections of batoclimab 680 mg for 2 weeks, followed by 340 mg for 4 weeks. In the double-blind trial, patients were randomized 2:2:1:2 to weekly batoclimab (680 mg, 340 mg, 255 mg) or placebo for 12 weeks.

Main Outcome: Change from baseline in serum anti-TSH-R-Ab and total IgG (POC); 12-week proptosis response (randomized trial).

Results: The randomized trial was terminated because of an unanticipated increase in serum cholesterol; therefore, data from 65 of the planned 77 patients were analyzed. Both trials showed marked decreases in pathogenic anti-TSH-R-Ab and total IgG serum levels ($P < .001$) with batoclimab. In the randomized trial, there was no statistically significant difference with batoclimab vs placebo in proptosis response at 12 weeks, although significant differences were observed at several earlier timepoints. In addition, orbital muscle volume decreased ($P < .03$) at

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The Journal of Clinical Endocrinology & Metabolism, 2023, Vol. 108, No. 12 **3123**

12 weeks, whereas quality of life (appearance subscale) improved ($P < .03$) at 19 weeks in the 680-mg group. Batoclimab was generally well tolerated, with albumin reductions and increases in lipids that reversed upon discontinuation.

Conclusions: These results provide insight into the efficacy and safety of batoclimab and support its further investigation as a potential therapy for TED.

Key Words: neonatal fragment crystallizable receptor, FcRn, batoclimab, thyroid eye disease, thyrotropin receptor autoantibodies, immunoglobulin G

Abbreviations: AE, adverse event; Ab, antibody; CAS, clinical activity score; CT, computed tomography; EUGOGO, European Group on Graves' Orbitopathy; FcRn, neonatal fragment crystallizable receptor; FT3, free triiodothyronine; FT4, free thyroxine; GO-QoL, Graves' orbitopathy Quality of Life score; ITT, intent to treat; LDL-C, low-density lipoprotein cholesterol; POC, proof-of-concept; QoL, quality of life; TED, thyroid eye disease; TSH, thyrotropin; TSH-R, TSH receptor.

IgG autoantibodies (Ab) target TSH receptors (TSH-R) on the thyroid gland and orbital target cells, causing Graves' disease and associated thyroid eye disease (TED) (1-3). These pathogenic and disease-specific anti-TSH-R-Ab lead to activation of orbital fibroblasts via TSH-R- and IGF-1 receptor–mediated pathways, inducing local inflammation and hydrophilic mucopolysaccharide production, and resulting in tissue edema, extraocular muscle swelling, and expansion of orbital connective tissue (4, 5). Common features of TED include lid retraction, congestion, redness and swelling of the eyelids and conjunctiva, proptosis, diplopia, and, occasionally, visual impairment from optic nerve compression (6). TED has a negative impact on quality of life (QoL) through its effects on appearance and visual function, which may disrupt both social and work life; has an acknowledged public health relevance; and may become sight-threatening (6-8).

The neonatal fragment crystallizable receptor (FcRn) is a unique cellular receptor with an affinity for IgG and albumin, 2 completely unrelated plasma proteins (9, 10). Both ligands bind the receptor at distinct binding sites in a remarkably similar pH-dependent manner, which is fundamental for the versatile functions spanning both immunological and nonimmunological processes (11, 12). FcRn is broadly expressed and functions in both hematopoietic and nonhematopoietic cells, including specialized cell types of vital organs such as the kidneys, liver, and placenta, which highlights the importance of the receptor in the homeostatic regulation of the ligands throughout the body (13). The FcRn functions as a recycling mechanism to prevent degradation and extend the half-life of IgG and albumin in circulation. Several FcRn inhibitors selectively targeting IgG recycling are now moving rapidly toward clinical practice in neurology and hematology (14, 15). These molecules accelerate the destruction of IgG, reducing pathogenic IgG and IgG immune complexes, with no anticipated effects on IgA, IgM, IgE, complement, plasma cells, B cells, or other cells of the innate or adaptive immune systems. Hence, FcRn inhibitors have the potential for future use in a much wider variety of antibody-mediated autoimmune diseases (16).

Batoclimab (IMVT-1401) is a selective, fully human monoclonal antibody with high affinity for the IgG-binding site on FcRn (17). By competitively binding to the IgG binding site on FcRn, batoclimab blocks FcRn-mediated recycling of IgG, resulting in enhanced degradation and subsequent reductions in IgG levels (Fig. 1) (15). This translates to clinical benefits in patients with TED by reducing the level of pathogenic IgG anti-TSH-R-Ab. This manuscript describes the first clinical trials of batoclimab in patients with clinically active, moderate-to-severe TED.

Methods

Proof-of-concept Trial

Trial design and patients

The proof-of-concept (POC), phase 2a, open-label single-arm trial was conducted at 4 sites in Canada (NCT03922321). The primary objectives were to assess the safety, tolerability, and pharmacodynamic effects of batoclimab. Batoclimab was administered as a weekly 680-mg subcutaneous injection for 2 weeks, followed by a weekly 340-mg subcutaneous injection for 4 weeks; the follow-up period was 11 weeks (Supplementary Fig. 1A (18)). Key enrollment criteria included age ≥18 years, a clinical diagnosis of Graves' disease associated with moderate-to-severe, active TED, and a clinical activity score (CAS) of ≥4 for the most severely affected eye at screening and baseline. Patients were required to have an onset of TED within 9 months of screening and documented evidence of detectable anti-TSH-R-Ab at screening. Complete enrollment criteria are available at https://clinicaltrials.gov/ct2/show/NCT03922321.

Procedures

Following the initial dose at baseline, visits occurred on days 3 and 5, and then weekly thereafter throughout the treatment period. Following the final dose, 2 visits occurred on days 38 and 40, with weekly visits thereafter through 11 weeks postbaseline and every other week until 17 weeks postbaseline. Pharmacodynamic changes in serum IgG and anti-TSH-R-Ab were monitored weekly during the treatment period.

Outcomes

The primary pharmacodynamic endpoints included change from baseline to 6 weeks postbaseline in serum anti-TSH-R-Ab, total IgG, and 4 IgG subclasses, which were summarized as mean change from baseline and mean percent change from baseline by visit and treatment group. Secondary and exploratory endpoints included the proportion of patients achieving proptosis response (≥2-mm reduction in study eye proptosis without a ≥2-mm increase in fellow eye), CAS response (score of 0 or 1), and diplopia response (improvement of ≥1 grade of the Gorman diplopia score). Safety endpoints included adverse events (AEs) and changes from baseline in vital signs, clinical laboratory values, and electrocardiograms.

Randomized, Placebo-controlled, Double-blind Trial

Trial design and patients

The multicenter, randomized, double-blind, placebo-controlled, phase 2b trial was conducted at 19 sites in Canada, Europe, and the United States (NCT03938545) to assess 3 batoclimab dosing regimens (680 mg, 340 mg, and 255 mg) vs placebo administered weekly for 12 weeks (Supplementary Fig. 1B (18)). The primary objectives were to examine the effects of batoclimab vs placebo on proptosis response rate at 12 weeks postbaseline and assess the safety and tolerability in patients with moderate-to-severe, active TED. Enrollment criteria for the randomized trial, which were similar to the POC study, are available at https://clinicaltrials.gov/ct2/show/NCT03938545.

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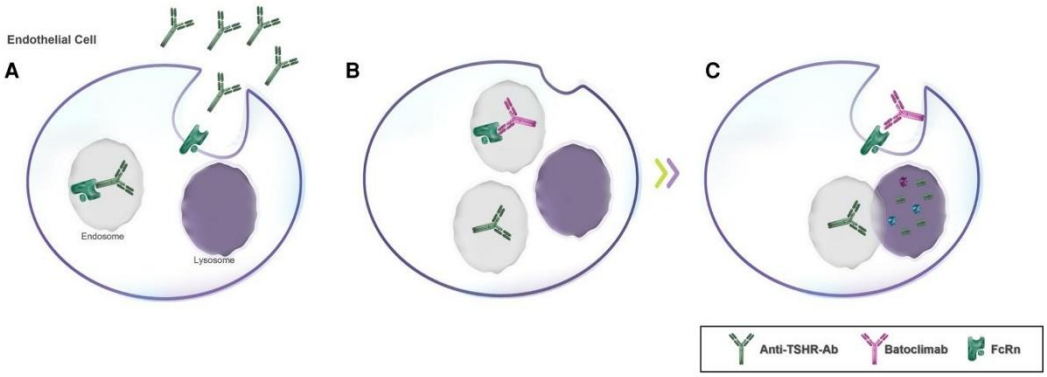

Figure 1. Batoclimab mechanism of action. (A) In the absence of batoclimab, FcRn binds to the anti-TSH-R-Ab, inhibiting their degradation and returning them into the circulation. (B) With batoclimab, FcRn is blocked from binding to anti-TSH-R-Ab. (C) Anti-TSH-R-Ab are transported to the lysosome for degradation, decreasing their levels in the circulation. TSH-R, thyrotropin receptor.

Procedures

Eligible patients were randomized 2:2:1:2 via an interactive web response system to weekly subcutaneous injections of batoclimab (680 mg, 340 mg, or 255 mg) or placebo. The randomization ratio was determined based on expected average total IgG reductions of approximately 75% to 80%, 65% to 70%, and 45% to 55% in the batoclimab 680-mg, 340-mg, and 255-mg arms, respectively, after 4 to 5 doses. Given the anticipated lower impact on IgG with the 255-mg dose, and the prediction that IgG reductions of >50% would be needed for clinical benefits, the trial was designed to focus on the higher doses, while still collecting enough data for the 255-mg dose to characterize potential benefits. Randomization was stratified by current smoking status ("yes" or "no"). Visits occurred weekly throughout the treatment period; following the final dose, visits occurred at 12, 13, 15, and 19 weeks postbaseline, including a 7-week follow-up period.

Total IgG was measured at Eurofins (Lancaster, PA, USA, and Breda, Netherlands). All pharmacodynamic TSH-R-Ab samples were analyzed at the accredited and certified Thyroid Lab of the Johannes Gutenberg University Medical Center (Mainz, Germany). Because changes in IgG, albumin, total protein, alkaline phosphatase, and antibody laboratory data could potentially be unblinding, investigators and study site personnel were blinded to these data during the study, and levels were monitored by an unblinded medical monitor. Lipid panels were measured at baseline and at 11 and 17 weeks postbaseline.

Orbital imaging was conducted at 10 participating sites. Orbital computed tomography (CT) was used to measure orbital muscle volume at baseline and in patients considered to be proptosis responders at 12 weeks postbaseline. CT scans were collected locally at each site and provided to a central reader for analysis (University of Michigan, Ann Arbor, MI, USA). The cases were annotated by a validated graphic user interface tool, MiViewer, which was developed in the CAD-AI Research Laboratory at the Department of Radiology at the University of Michigan, and that can annotate, outline, and measure the volume of anatomical organs. One board-certified radiologist marked all volumes of interest on all consecutive coronal CT images of the orbit by manually tracing the margins of the 5 major extraocular muscles, the 4 recti and the superior oblique, to calculate overall muscle volume.

Outcomes

The primary efficacy endpoint was the proptosis responder rate at 12 weeks postbaseline, defined as a ≥2-mm reduction in study eye proptosis without ≥2-mm increase in fellow eye. The study eye was defined as the most severely affected eye at baseline in terms of proptosis, or if both eyes were equally affected, the right eye was used as the study eye. Proptosis was assessed for each patient using the same Hertel instrument, supplied by the sponsor.

Secondary endpoints included the percent change from baseline in TSH-R-Ab, total IgG, and IgG subclasses at 12 weeks postbaseline. Exploratory endpoints included proptosis responder rates at all other scheduled timepoints; CAS responder rate, defined as proportion of patients with CAS of 0 or 1; change from baseline in Gorman Score for diplopia and the European Group on Graves' Orbitopathy (EUGOGO) Graves' orbitopathy Quality of Life (GO-QoL) total score, as well as visual functioning and appearance subscale scores (1); CT-measured orbital muscle volume; and change from baseline in levels of free triiodothyronine (FT3) and free thyroxine (FT4). Similar to the POC, safety outcomes included AE and changes from baseline in vital signs, clinical laboratory values, and electrocardiograms.

Ethics

Both trials were approved by the ethics committee at each center and conducted in accordance with the International Council for Harmonization Good Clinical Practice Guideline. All patients were required to provide written informed consent.

Statistical Analyses

The sample size for the POC was determined using clinical and recruitment considerations to achieve approximately 8 evaluable patients. For the randomized trial, sample size considerations for the proptosis responder rate assumed a 5% response rate in the placebo arm and a 50% response rate in

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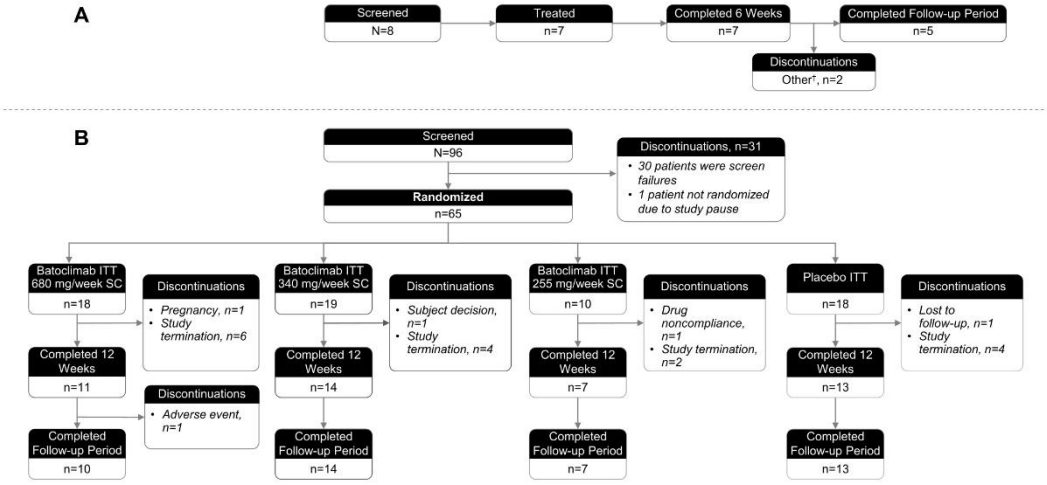

Figure 2. CONSORT diagram. (A) POC. (B) Randomized trial*. ITT, intent to treat, defined as patients who received ≥1 dose and had ≥1 post-baseline visit. POC, proof-of-concept. *One patient missed a total of 3 doses because of COVID-19 infection. Additionally, 2 patients had their 12-week postbaseline visit as a video appointment because of COVID-restrictions and did not have clinical assessments completed at that visit. The 7-week follow-up period was completed by 44 (67.7%) patients. †Patients could not attend clinic visits.

the 680-mg arm. Considering an anticipated dropout rate of 15%, 22 patients were planned to be randomized to the 680-mg, 340-mg, and placebo groups, with 19 patients per arm being sufficient to detect a between-group difference with 85% power using a 2-sided Fisher's exact test with an alpha level of .05. All analyses were performed using SAS Version 9.4 or higher (SAS Institute Inc, Cary, NC, USA).

In both trials, safety was evaluated in all patients who received ≥1 dose of batoclimab or placebo. AE were coded using the Medical Dictionary for Regulatory Activities (MedDRA Version 21.1) and summarized descriptively. The severity (mild [1], moderate [2], severe/medically significant [3], life-threatening [4], death [5]) and causality (probably, possibly, not related) of all AEs were assessed by the investigators.

In the POC, pharmacodynamic endpoints were evaluated in all patients who had a baseline measure, along with a postbaseline measure, and received ≥1 dose of batoclimab. Data are reported as observed and summarized descriptively.

In the randomized trial, pharmacodynamic and clinical efficacy endpoints were determined using the intent-to-treat (ITT) population, including all randomized patients who received ≥1 dose of batoclimab or placebo and had ≥1 postbaseline visit. Data are reported as observed, and all significance levels are considered nominal. For the proportion of proptosis responders, each dose group was compared with the placebo group using a stratified Mantel-Haenszel test with smoking status as a stratification factor. Changes from baseline in proptosis and CAS were analyzed using a mixed model for repeated measures approach. The least-square mean differences and corresponding 95% CIs were reported.

Results

Proof-of-concept Trial

In the POC, 7 patients met the eligibility criteria (Fig. 2A). All 7 patients completed the 6-week treatment period and 5 (71.4%) completed the 12-week follow-up phase. No patient discontinued treatment or withdrew because of an AE; 2 patients withdrew during the follow-up period because of an inability to attend clinic visits. Patient demographics and baseline characteristics are shown in Table 1. Batoclimab was associated with decreases in total serum IgG (Fig. 3A) and IgG subclasses (Supplementary Fig. 2 (18)). There were significant mean percent reductions in total ($P \leq .005$) and stimulatory ($P < .05$) TSH-R-Ab levels during the treatment period, which increased toward baseline levels during the follow-up period (Figs. 3B and 3C). The numbers of patients achieving a proptosis response, a CAS response or a diplopia response are included in Supplementary Table 1 (18). Up to 3 patients achieved a proptosis response, a CAS response, or a diplopia response during the treatment or follow-up periods.

All AEs were mild or moderate, and no serious AEs, discontinuations because of AEs, or deaths occurred (Table 2). There were no clinically significant changes in hematology parameters or infection-related AEs during the treatment period. Mean albumin concentrations decreased by 1 week postbaseline and returned to baseline levels by the end of the follow-up period. Two patients with normal albumin concentrations at baseline had values below the normal range during dosing, which returned to the normal range during the follow-up period. No patient had an albumin level <25 g/L at any point during the study.

Randomized, Placebo-controlled, Double-blind Trial

The planned population was 77 randomized patients. Based on a composite review and data suggesting an unanticipated drug-related effect on lipids, the trial was paused and subsequently terminated; an interim analysis was conducted when 65 patients had been randomized and were included in the safety and ITT populations (Fig. 2B). At the time of the pause, 45 patients (69.2%) had completed the 12-week treatment

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Table 1. Baseline demographics, clinical status, and quality of life

		Randomized trial					
	POC	Batoclimab					
Characteristic	Batoclimab N = 7	680 mg n = 18	340 mg n = 19	255 mg n = 10	Placebo n = 18	Total N = 65	*P* value[a]
Baseline characteristics							
Age (y)							.15
Mean (SD)	56.7 (14.94)	46.6 (9.0)	52.4 (8.1)	44.3 (12.6)	46.1 (12.5)	47.8 (10.6)	
Median (min, max)	54.0 (42, 80)	47.5 (26, 58)	53.0 (28, 63)	41.0 (23, 66)	43.5 (26, 73)	50.0 (23, 73)	
Female, n (%)	4 (57.1)	15 (83.3)	13 (68.4)	8 (80.0)	14 (77.8)	50 (76.9)	.74
Race, n (%)							.67
Asian	1 (14.3)	0	0	0	0	0	
White	6 (85.7)	17 (94.4)	18 (94.7)	10 (100)	18 (100)	63 (96.9)	
Not reported	0	1 (5.6)	1 (5.3)	0	0	2 (3.1)	
Ethnicity, n (%)							.41
Hispanic or Latino	0	1 (5.6)	2 (10.5)	0	0	3 (4.6)	
Not Hispanic or Latino	6 (85.7)	17 (94.4)	17 (89.5)	10 (100)	18 (100)	62 (95.4)	
Not reported	1 (14.3)	0	0	0	0	0	
Smoking status, n (%)							.34
Never	3 (42.9)	6 (33.3)	10 (52.6)	4 (40.0)	3 (16.7)	23 (35.4)	
Former	2 (28.6)	9 (50.0)	6 (31.6)	5 (50.0)	13 (72.2)	33 (50.8)	
Current	2 (28.6)	3 (16.7)	3 (15.8)	1 (10.0)	2 (11.1)	9 (13.8)	
Smoking pack-years, mean (SD)[b]	10.8 (9.4)	14.4 (12.4)	15.5 (16.4)	20.34 (19.9)	12.1 (11.2)	14.7 (13.9)	.68
BMI (kg/m^2), mean (SD)	25.3 (4.0)	26.1 (4.7)	27.1 (4.5)	25.1 (2.8)	26.2 (4.3)	26.3 (4.3)	.69
Thyroid status, n (%)[c]							
Hyperthyroid	1 (14.3)	5 (27.8)	3 (15.8)	5 (50.0)	2 (11.1)	15 (23.1)	
Euthyroid	6 (85.7)	10 (55.6)	13 (68.4)	5 (50.0)	11 (61.1)	39 (60.0)	
Hypothyroid	0	3 (16.7)	3 (15.8)	0	5 (27.8)	11 (16.9)	
History of RAI therapy	4 (57.1)	0	0	1 (10.0)	0	1 (1.5)	
History of thyroidectomy	1 (14.3)	1 (5.6)	1 (5.3)	2 (20.0)	2 (11.1)	6 (9.2)	
Concomitant thyroid medications, n (%)							0.35
Thionamide antithyroid drugs	2 (28.6)	6 (33.3)	10 (52.6)	4 (40.0)	11 (61.1)	31 (47.7)	
Ophthalmic parameters							
Proptosis (mm), mean (SD)	23.1 (3.34)	22.7 (3.1)	23.0 (4.0)	22.3 (2.9)	22.7 (2.7)	22.7 (3.2)	.96
Proptosis severity, n (%)							.86
<20 mm	1 (14.3)	2 (11.1)	4 (21.1)	3 (30.0)	3 (16.7)	12 (18.5)	
20-23 mm	3 (42.9)	10 (55.6)	7 (36.8)	4 (40.0)	9 (50.0)	30 (46.2)	
>23 mm	3 (42.9)	6 (33.3)	8 (42.1)	3 (30.0)	6 (33.3)	23 (35.4)	
CAS, mean (SD)	5.4 (1.13)	4.8 (0.9)	5.1 (0.9)	4.9 (1.0)	5.2 (1.0)	5.0 (0.9)	.70
Gorman diplopia score, n (%)							.27
No diplopia	1 (14.3)	8 (44.4)	9 (47.4)	4 (40.0)	5 (27.8)	26 (40.0)	
Grade I—intermittent diplopia	3 (42.9)	3 (16.7)	2 (10.5)	2 (20.0)	1 (5.6)	8 (12.3)	
Grade II—inconstant diplopia	3 (42.9)	1 (5.6)	4 (21.1)	4 (40.0)	7 (38.9)	16 (24.6)	
Grade III—constant diplopia	0	6 (33.3)	4 (21.1)	0	5 (27.8)	15 (23.1)	
QoL							
GO-QoL, mean (SD)							
Total score	59.8 (21.5)	53.3 (25.4)	62.4 (15.6)	60.2 (19.3)	60.0 (24.3)	58.9 (21.5)	.62
Visual functioning subscale	61.5 (24.7)	59.0 (31.7)	65.9 (24.1)	60.4 (23.9)	63.1 (26.9)	62.4 (26.6)	.88
Appearance subscale	58.0 (25.2)	47.6 (22.9)	58.9 (27.3)	60.0 (21.7)	56.9 (28.1)	55.4 (25.5)	.49

Abbreviations: BMI, body mass index; CAS, clinical activity score; GO-QoL, EUGOGO Graves' orbitopathy Quality of Life questionnaire; POC, proof-of-concept; QoL, quality of life; RAI, radioactive iodine.
[a]Overall *P* value for differences in baseline demographics and disease characteristics among randomized treatment groups were assessed using the χ^2 test for categorical variables and ANOVA for continuous variables.
[b]Pack years = packs multiplied by years of smoking = cigarettes per day/pack size (20) multiplied by years of smoking (days of smoking/365.24) in current smokers.
[c]Thyroid status based on serum T3/T4 normal range. Patients were eligible if T3/T4 serum levels were <50% above or below normal levels at screening.

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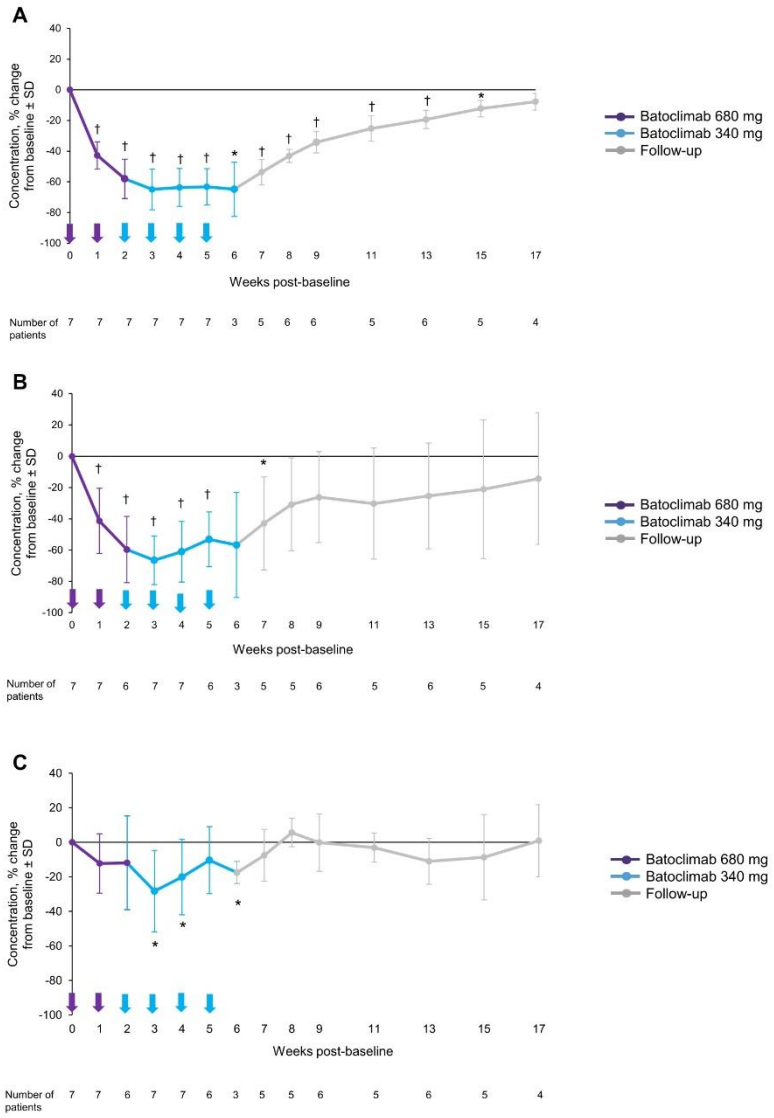

Figure 3. Serological results from POC. (A) Change in total IgG. (B) Change in total anti-TSH-R antibodies. (C) Change in stimulatory anti-TSH-R antibodies. POC, proof-of-concept; TSH-R, TSH receptor. Arrows indicate week of treatment. $^{*}P < .05$ for change from baseline (*t* test). $^{\dagger}P \leq .005$ for change from baseline (*t* test).

period and 2 had withdrawn. A total of 18 (27.7%) patients were receiving treatment and discontinued drug dosing because of the pause but were asked to complete the 7-week follow-up period; 44 patients (67.7%) completed the follow-up period (Supplementary Table 2 (18)). Baseline characteristics were similar across treatment groups with a few exceptions (Table 1). There was a higher number of patients with diplopia at baseline in the placebo (72.2%) vs batoclimab groups (52.6%-60.0%; Supplementary Table 3 (18)), including constant/inconstant diplopia, which was present in 12/18 (66.7%) placebo patients compared with 7/18 (38.9%) patients in the batoclimab 680-mg group.

There was an early (2 weeks) and marked (30%-60%) dose-related reduction in total IgG in all 3 batoclimab groups ($P < .001$) vs placebo (Fig. 4A). Similar dose-related decreases were also observed for each IgG subclass (Supplementary Fig. 3 (18)). More specifically, there was an early, marked, and dose-related reduction in total (binding) anti-TSH-R-Ab (disease biomarkers) with a nadir at 12 weeks postbaseline ($P < .001$ for batoclimab 680 and 340 mg and $P < .05$ for

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Table 2. Summary of AEs in the POC and randomized trials

		Randomized trial				
	POC	Batoclimab				Total
	Batoclimab n = 7	680 mg n = 18	340 mg n = 19	255 mg n = 10	Placebo n = 18	Total N = 72
Any AEs, n (%)	7 (100)	16 (88.9)	16 (84.2)	8 (80.0)	16 (88.9)	63 (87.5)
Treatment-related AEs[a], n (%)	6 (85.7)	13 (72.2)	14 (73.7)	5 (50.0)	10 (55.6)	48 (66.7)
Grade ≥3 AEs, n (%)	0	1 (5.6)	0	1 (10.0)	1 (5.6)	3 (4.2)
Serious AEs, n (%)	0	0	0	1 (10.0)	0	1 (1.4)
Discontinuation of study drug because of AEs, n (%)	0	0	0	0	0	0
AEs in ≥2 patients in any group, n (%)						
Injection-site erythema	0	9 (50.0)	9 (47.4)	3 (30.0)	3 (16.7)	24 (33.3)
Lethargy	0	2 (11.1)	5 (26.3)	1 (10.0)	4 (22.2)	12 (16.7)
Injection-site swelling	0	1 (5.6)	4 (21.1)	1 (10.0)	1 (5.6)	7 (9.7)
Nausea	0	0	4 (21.1)	0	2 (11.1)	6 (8.3)
Fatigue	2 (28.6)	0	2 (10.5)	1 (10.0)	0	5 (6.4)
Muscle spasms	1 (14.3)	1 (5.6)	3 (15.8)	0	0	5 (6.4)
Edema peripheral	0	5 (27.8)	0	0	0	5 (6.4)
Intraocular pressure increased	0	2 (11.1)	0	0	2 (11.1)	4 (5.6)
Injection-site pain	0	1 (5.6)	3 (15.8)	0	0	4 (5.6)
Abdominal pain upper	0	1 (5.6)	2 (10.5)	0	0	3 (4.2)
Vomiting	0	0	2 (10.5)	0	1 (5.6)	3 (4.2)
Arthralgia	0	0	0	1 (10.0)	2 (11.1)	3 (4.2)
Blood cholesterol increased	0	0	2 (10.5)	0	0	2 (2.8)
Lacrimation increased	2 (28.6)	0	0	0	0	2 (2.8)
Dizziness	2 (28.6)	0	0	0	0	2 (2.8)

In the POC study, 1 patient experienced moderate fatigue that was considered probably related to study drug and moderate palpitations that were considered possibly related to study drug, leading to a 1-week interruption of dosing. The most frequently reported AEs, occurring in 2 patients each, were dizziness, fatigue, and increased lacrimation. Ocular AEs were reported in 5 patients, with 1 patient each experiencing diplopia, eye irritation, eye pain, eye swelling, keratopathy, ocular hyperemia, superior limbic keratoconjunctivitis, and swelling of the eyelid. One patient experienced hypotension, which was assessed as mild in severity and possibly related to study drug; the hypotension resolved without intervention or discontinuation of study drug. In the randomized trial, the majority (53/56 [94.6%]) of AEs were mild in severity. One patient receiving batoclimab 680 mg experienced 7 AEs of moderate injection-site swelling and 1 patient receiving batoclimab 340 mg experienced 2 AEs of moderate erythema. All injection-site AEs in the batoclimab 255 mg and placebo groups were mild, and none was reported as severe in any treatment group. Three patients in the batoclimab 680-mg group had albumin levels <25 g/L at some point during the study but did not experience an AE of peripheral edema. Modest increases in alkaline phosphatase were seen in the batoclimab treatment groups with an apparent dose response. Among patients with normal alkaline phosphatase at baseline, 8, 5, 1, and 5 patients had postbaseline elevations greater than upper limit of normal in the batoclimab 680-mg, 340-mg, and 255-mg and placebo groups, respectively, of which 1 patient (batoclimab 680 mg) had aspartate aminotransferase and alanine transaminase elevations less than 2 times upper limit of normal. No patient had concomitant elevations in gamma-glutamyl transferase or bilirubin, and no patient had alkaline phosphatase elevations greater than 2 times the upper limit of normal.
Abbreviations: AE, adverse event; POC, proof-of-concept.
[a]Includes all events reported as "probably related," "possibly related," or missing relationship to study drug.

255 mg vs placebo; Fig. 4B). Functional stimulatory anti-TSH-R-Ab also decreased, with significant reductions ($P < .001$) from weeks 2 through 11 postbaseline in the batoclimab 680-mg and 340-mg groups vs placebo (Fig. 4C).

A numerically greater number of batoclimab-treated patients achieved a proptosis response vs placebo ($P < .05$) at multiple timepoints (weeks 4, 5, and 11 postbaseline in the 680-mg group and weeks 5, 9, 11, and 13 postbaseline in the 340-mg group). However, no significant differences in proptosis responder rates between the batoclimab and placebo groups were seen at the 12-week primary endpoint (Fig. 5A), likely because of fewer patients with available data at that timepoint. Of the 15 patients who were proptosis responders at 9 and/or 11 weeks postbaseline, 14 were on batoclimab. Four batoclimab-treated patients did not have a measurement at the primary endpoint including 2 patients in the batoclimab 680-mg group, 1 in the 340-mg group, and 1 in the 255-mg group because of either study termination (n = 3) or remote office visits resulting from COVID restrictions (n = 1). A significant difference in CAS response (score of 0 or 1 only) was also observed in the batoclimab treatment groups ($P < .05$) at weeks 7 (255 mg) and 11 (680 mg) postbaseline compared with placebo (Fig. 5B). No changes from baseline in the Gorman score for diplopia were observed (Supplementary Table 3 (18)).

The EUGOGO GO-QoL appearance subscale was significantly improved at 19 weeks postbaseline with batoclimab 680 mg ($P < .03$ vs placebo). In addition, a relevant improvement of both GO-QoL total score and appearance subscale (≥6 points) was noted in the 2 highest batoclimab groups at 12 and 19 weeks postbaseline. In contrast, no changes were observed in placebo-treated patients (Supplementary Table 4 (18)).

Paired CT scans from baseline and 12 weeks postbaseline were available for 11 patients (Fig. 6). Dose-related,

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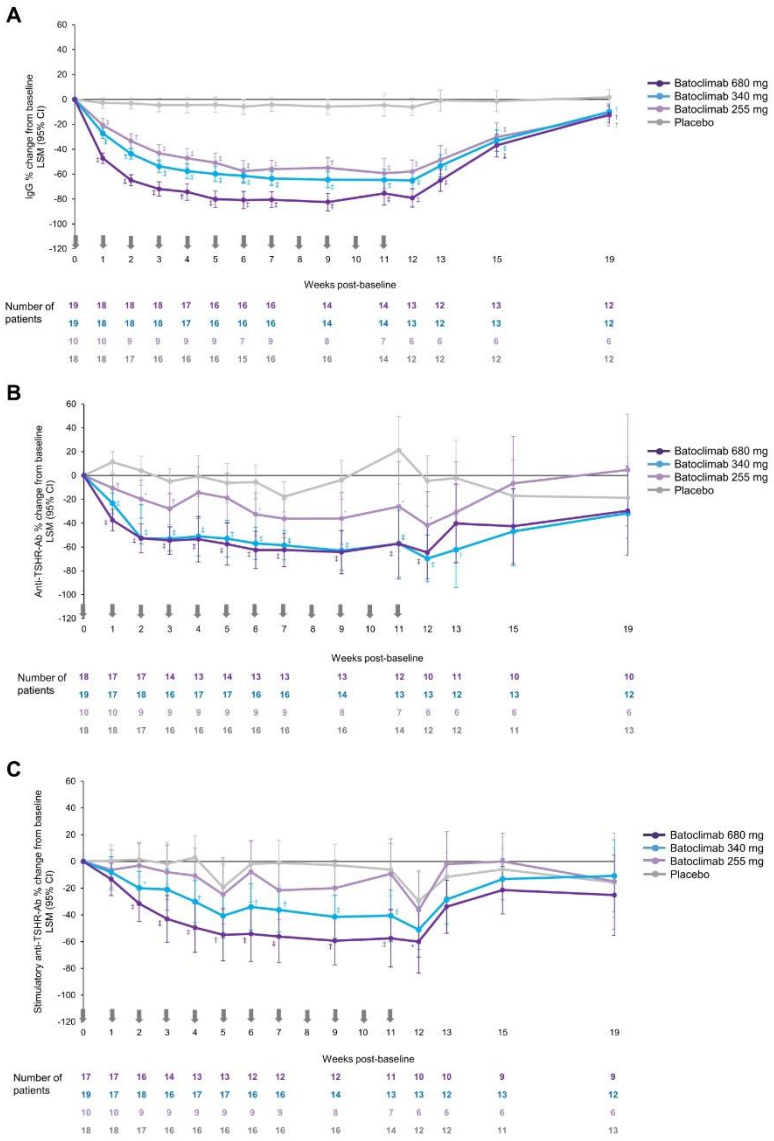

Figure 4. Serological results in the randomized trial (ITT population). (A) Change in total IgG. (B) Change in total anti-TSH-R antibodies. (C) Change in stimulatory anti-TSH-R antibodies. ITT, intent-to-treat, defined as patients who received ≥1 dose and had ≥1 postbaseline visit; LSM, least-square mean; TSH-R, TSH receptor. Arrows indicate week of treatment. $^{*}P < .05$ vs placebo. $^{\dagger}P < .01$ vs placebo. $^{\ddagger}P < .001$ vs placebo.

significant ($P < .03$) reductions in orbital muscle volume in the study eye were observed at 12 weeks postbaseline for batoclimab 680 and 340 mg compared with placebo. Supplementary Fig. 4 (18) shows imaging of the orbital muscle in a patient treated with batoclimab 680 mg at baseline and 12 weeks postbaseline.

Reductions in FT3 and FT4 were observed during the study, with statistically significant changes vs placebo seen as early as week 1 for the 680-mg dose and week 2 for all batoclimab doses (Supplementary Fig. 5 (18)). Significant reductions in FT3 vs placebo were observed in the highest dose group through week 7, and for FT4, to week 3.

Most treatment-emergent AEs were mild or moderate and there were no deaths (Table 2). Severe (grade 3) AEs were reported in 3 patients, 1 each treated with batoclimab 680 mg (upper abdominal pain, probably related), batoclimab

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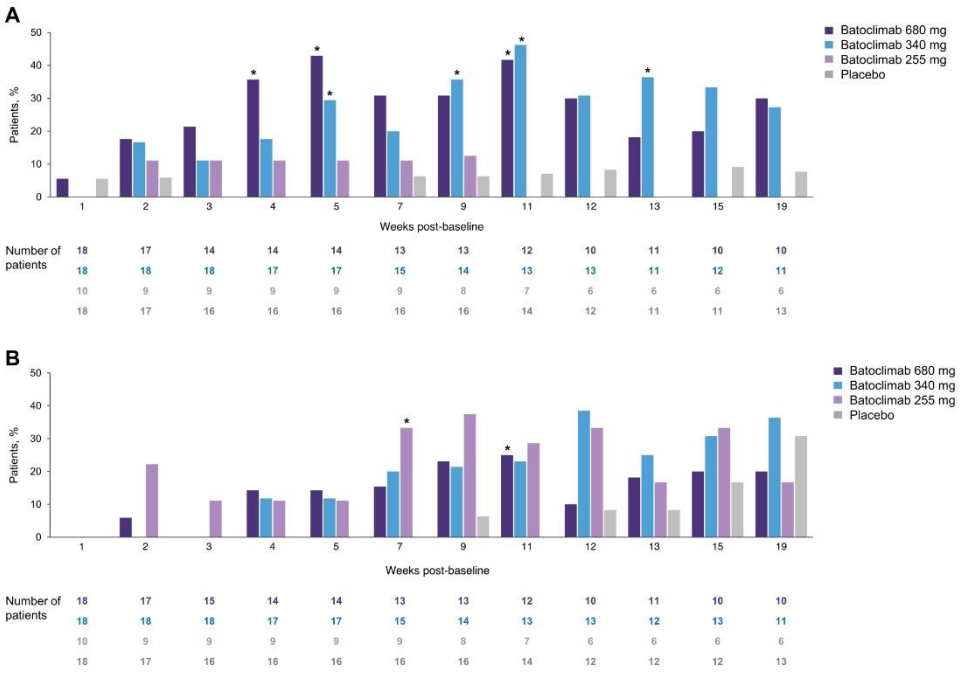

Figure 5. Proptosis and CAS responders in the randomized trial (ITT population). (A) Proptosis responders. (B) CAS responders. CAS, clinical activity score of TED. ITT, intent-to-treat, defined as patients who received ≥1 dose and had ≥1 postbaseline visit. *$P < .05$ vs placebo.

255 mg (optic neuropathy, not related), and placebo (headache, not related). Grade 3 optic neuropathy was the only severe AE reported during the treatment period and was not considered treatment-related. One patient who had received batoclimab 680 mg developed grade 3 autoimmune encephalitis a few weeks after a COVID infection during the follow-up period (18 weeks postbaseline); this event was also not considered treatment-related.

The most commonly reported AEs are listed in Table 2. Five patients in the batoclimab 680-mg group experienced peripheral edema, of which 2 patients had edema considered moderate in severity. Four of the 5 patients who experienced peripheral edema recovered without interruption of study drug. In 1 patient, the edema led to drug interruption, and the patient recovered and was restarted on therapy; this patient experienced reductions in serum albumin 5 to 9 weeks postbaseline (25-29 g/L), which returned to normal by 11 weeks. There was a reversible, dose-related reduction in serum albumin in patients treated with batoclimab (Fig. 7A). Twelve patients in the batoclimab 680-mg group and 3 patients in the 340-mg group had serum albumin levels below the lower limit of normal (32 g/L) at least once during the study, whereas no patients in the 255-mg or placebo groups had albumin levels <32 g/L during the study. There were no AEs of hypoalbuminemia, and by 19 weeks postbaseline all treatment groups returned to near baseline levels. Furthermore, there were no clinically significant changes in hematology parameters. No patients had elevations of greater than 2 times the upper limit of normal in alanine transaminase, aspartate aminotransferase, or bilirubin. Following the trial pause, the post hoc analysis revealed a dose-related increase in low-density lipoprotein cholesterol (LDL-C) at week 11 postbaseline (58.9%, 29.2, 16.7%, and −3.1% in the batoclimab 680-mg, 340-mg, 255-mg, and placebo groups, respectively), with increases reversible within 8 weeks of discontinuation (Fig. 7B).

Discussion

These trials provide the first clinical evidence demonstrating the impact of the innovative concept of FcRn inhibition in TED, and specifically highlight the potential efficacy and safety of batoclimab, a fully human anti-FcRn monoclonal antibody administered as a low-volume subcutaneous injection. In the POC, rapid reductions in IgG anti-TSH-R-Ab concentrations were evident within 1 week after the first dose. Moreover, proptosis, diplopia, and CAS responses (with scores of 0 or 1, assessed as disease inactivation), were noted at several timepoints. Together, these findings provided proof of concept for the randomized, placebo-controlled, dose-finding trial.

In the randomized trial, batoclimab treatment was associated with significant decreases in IgG anti-TSH-R-Ab levels. Serological results were mirrored by successful reduction of the eye muscle volume, supporting FcRn inhibition as an effective mechanism of action. Proptosis response was not significant at the primary 12-week endpoint, most probably because of the lack of available data on >25% of batoclimab patients who were previously responders but were not included in the primary assessment because of the trial

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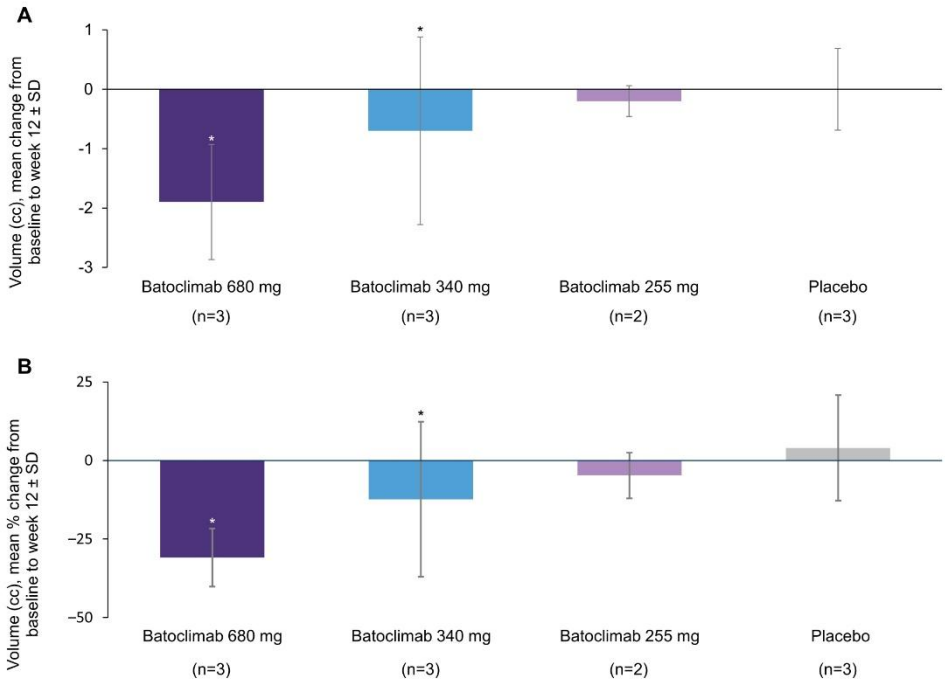

Figure 6. Changes in orbital muscle volume at 12 weeks postbaseline (ITT population). (A) Mean change. (B) Mean percent change. ITT, intent-to-treat, defined as patients who received ≥1 dose and had ≥1 post-baseline visit. *$P < .03$ vs placebo.

discontinuation and remote visits resulting from COVID restrictions. However, batoclimab was statistically significant vs placebo at multiple earlier timepoints, suggesting a relevant biological effect on disease-related measures. Consistent with these results, CAS responses were also noted at several timepoints during treatment; however, because inflammation can naturally improve over time, CAS is not necessarily a good marker of efficacy over the course of a trial. Moreover, improvements in CAS were also observed in the placebo group, making it difficult to assess treatment effects. The lack of observed effects on diplopia were likely driven by the low numbers of patients with diplopia at baseline, as well as the imbalance of patients with diplopia across groups, leading to insufficient statistical power to detect treatment effects. The GO-QoL appearance subscale significantly increased in the batoclimab 680-mg group at 19 weeks postbaseline, with mean improvements of ≥6 points for both GO-QoL subscales in the 680-mg and 340-mg study groups. Although these results are considered exploratory, they provide important insight into the potential for batoclimab as a treatment option for patients with TED.

Regarding safety, batoclimab was observed to be generally well tolerated; most AEs were mild or moderate, and no patients withdrew during the treatment periods because of AEs. Increases in LDL-C levels were likely related to reductions in serum albumin (10), which are expected based on the mechanism of action of batoclimab, and both were reversible following treatment discontinuation (14). FcRn recycles albumin through the same mechanism as IgG, helping to maintain levels by preventing transfer to the lysosome for degradation and delivering the proteins back into circulation (13). A correlation between changes in albumin and cholesterol has also been observed in hypoalbuminemic states, such as nephrotic syndrome (19-21) and congenital analbuminemia (22). The mechanistic pathways underlying this phenomenon have not yet been fully elucidated; however, limited evidence suggests that hepatocytes may respond to falling albumin levels by increasing production of apolipoprotein B (23). It is possible that a similar mechanism explains the increases in total cholesterol and LDL-C observed with batoclimab treatment. The extent to which LDL elevation can increase an individual's cardiovascular risk varies based on the magnitude of elevation, duration of exposure to the elevation, and the baseline risk of the patient (24). The relatively short, fixed duration of treatment in the batoclimab phase 3 trials reduces the risks of hypoalbuminemia and hypercholesterolemia. Preliminary evidence from a healthy volunteer study has demonstrated coadministration of a statin with batoclimab can prevent the lipid elevations (25).

The impact of batoclimab on thyroid function was examined as an exploratory endpoint, and statistically significant reductions were observed with batoclimab vs placebo for change from baseline in FT3 and FT4 at several timepoints. However, approximately half of the patients overall were receiving concomitant therapy with thionamide antithyroid drugs, and the rates of concomitant thyroid medication use were not equal across the different treatment groups. Therefore, although it is possible that batoclimab treatment may have an effect on associated Graves' disease, additional

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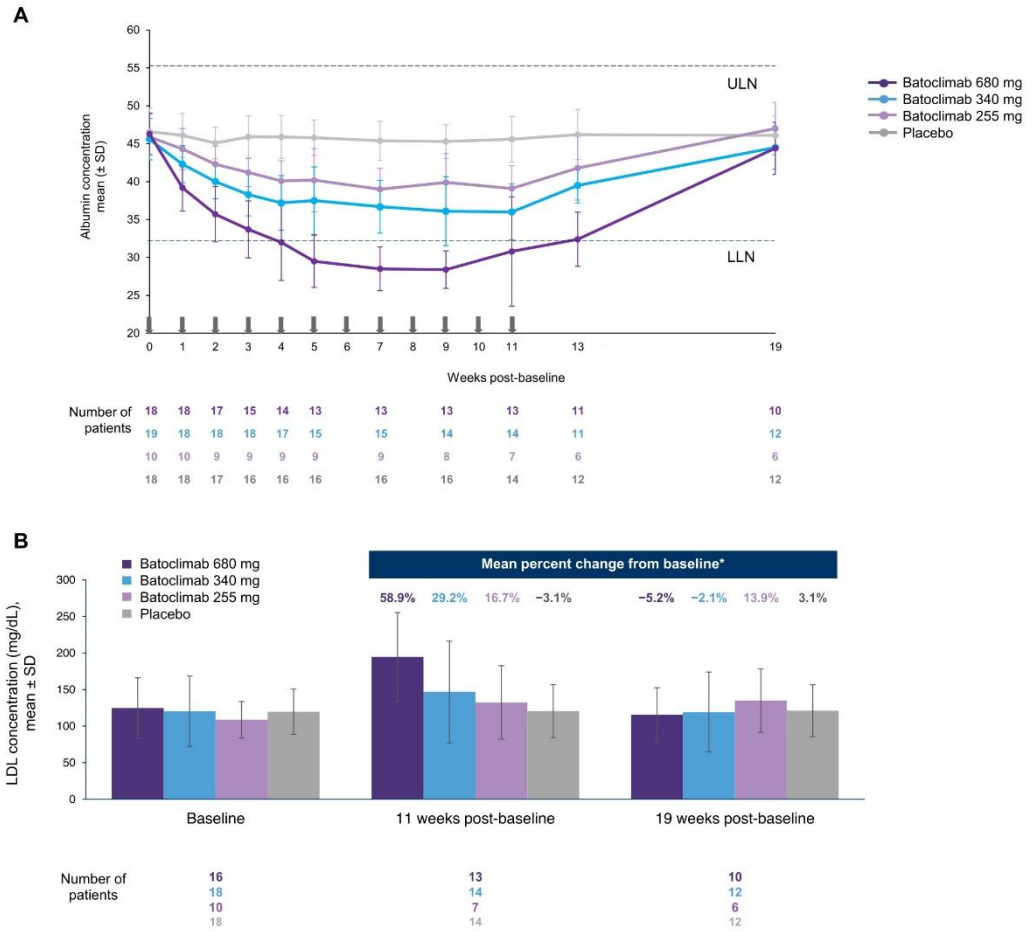

Figure 7. Changes in laboratory parameters in the randomized trial. (A) Change in serum albumin. (B) Change in LDL-C. LDL-C, low-density lipoprotein cholesterol; LLN, lower limit of normal; ULN, upper limit of normal. Arrows indicate week of treatment. Values above bars are percent (SD) change from baseline in patients who had values measured both at baseline and at the timepoint of interest. *In the batoclimab 680-mg group, 5/18 (27.8%) patients had LDL-C levels ≥160 mg/dL at baseline; at 12 weeks postbaseline, 2/18 (11.1%) had LDL-C levels ≥160 to <190 mg/dL and 6/18 (33.3%) had levels ≥190 mg/dL. In the 340-mg group, 1/19 (5.3%) and 2/19 (10.5%) patients had LDL-C levels of ≥160 to <190 mg/dL and ≥190 mg/dL, respectively, at baseline; at 12 weeks postbaseline, 4/19 (21.1%) and 3/19 (15.8%) had LDL-C levels of ≥160 to <190 mg/dL and ≥190 mg/dL, respectively. In the 255-mg group, no patients had LDL-C levels ≥160 mg/dL at baseline; at 12 weeks postbaseline, 2/10 (20.0%) had levels ≥190 mg/dL.

studies controlling for antithyroid medication use are needed to establish this.

Batoclimab may offer a novel treatment approach for moderate-to-severe, active TED. Specifically, batoclimab blocks FcRn from binding to anti-TSH-R-Ab, resulting in their degradation in the lysosome and reduction in circulation. Consequently, the activation of the TSH-R on orbital fibroblasts is expected to be reduced. In the trials presented here, batoclimab led to a rapid, marked, and significant decrease in serum TSH-R-Ab, with the serological nadir occurring at weeks 3 and 6 postbaseline in the POC and randomized trials, respectively—well before the primary endpoints were assessed. This is clinically relevant because the TSH-R is the primary autoantigen in both Graves' hyperthyroidism and TED, and TSH-R-Ab, especially stimulatory TSH-R-Ab, are acknowledged as the specific disease serological biomarker (26, 27).

Current guidelines, including the 2021 EUGOGO clinical practice guidelines (1) and the consensus statement of the American and European Thyroid Associations (28), recommend multidisciplinary management of TED; emphasize the long-standing, well-established role of high-dose IV glucocorticoids (29); and acknowledge the highly beneficial effects of the IGF-1– inhibiting monoclonal antibody, teprotumumab (30, 31). Further recommended treatment options include mycophenolate (32, 33), tocilizumab (34), rituximab (35), azathioprine (with or without orbital radiotherapy) (36, 37), and statins (38). Compared with these agents, the FcRn inhibitor batoclimab has the potential unique benefit of specifically targeting and markedly degrading pathogenic IgG TSH-R-Ab,

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with a likely dual benefit for both thyroid and eye autoimmune pathology (2, 19).

Limitations to the presented studies include the open-label nature and small number of subjects in the POC, as well as the early termination of the randomized trial and a lower than estimated sample size. A further limitation included the unanticipated dose-related increases in LDL-C; in future trials, the impact of changes in serum lipids will be closely assessed. Nevertheless, these are the first multicenter trials evaluating the efficacy and safety of this innovative treatment, and the results provide insight into the potential of FcRn inhibition and support further investigation of batoclimab as a therapy for TED. Valuable information on dose and duration of therapy were gained to design the upcoming phase 3 randomized, placebo-controlled 24-week trials (NCT05524571 and NCT05517421) and a 24-week open-label extension (NCT05517447).

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Author Contributions

G.J.K.: Principal investigator, critically analyzed and interpreted all submitted data, wrote the first draft, and reviewed and edited all further versions and revisions of the manuscript. P.J.D.: Principal investigator and critically reviewed all submitted data and edited the manuscript. A.S. and L.H.: Wrote the methodology for imaging, analyzed and interpreted all submitted computed tomography images, and critically reviewed the manuscript. J.X.: Performed all statistical analyses, wrote the statistical methods, and critically reviewed the manuscript. P.T., J.M.J., P.V., and W.L.M.: Critically reviewed, analyzed, and interpreted all submitted data and reviewed and edited the manuscript. J.W., B.C.G., H.M.E., A.P.J., D.J., E.A.B., M.N.S., A.E., S.P., C.V., S.T.W., J.N., N.T., M.S.S., S.E.F., C.C.N., I.H., M.A.S., and R.S.D.: Critically reviewed and edited the manuscript.

Disclosures

The sponsor (Immunovant, Inc.) participated in the design and conduct of the studies; the collection, management, analysis, and interpretation of the data; and the preparation of the manuscript. G.J.K.: The JGU Medical Center has received research-associated funding from Immunovant, Inc. and G.J.K. consults for Immunovant, Inc. P.J.D.: Unpaid consultant for Immunovant, Inc. and Sling Therapeutics. J.W., B.C.G., and H.M.E.: The JGU Medical Center has received research-associated funding from Immunovant, Inc. A.P.J.: Speaker for Horizon Therapeutics. M.N.S.: The Mayo Clinic has received research funding for the medical consulting activities performed by MNS for Immunovant, Inc., Horizon Therapeutics, and Sling Therapeutics. A.E.: Investigator for Novartis, Horizon Therapeutics, Immunovant, Inc., and Sling Therapeutics; advisor for Gensight; speaker for Sanofi and Novo Nordisk. S.T.W.: Consultant for Immunovant, Inc., and Sling Therapeutics; advisor for Horizon Therapeutics. J.N.: Advisor for Immunovant, Inc. M.S.S., J.M.J., and J.X.: Consultants for Immunovant, Inc. S.F.: Consultant for the Association of University Professors of Ophthalmology and member of the Board of Directors of Doheny Eye Institute; advisor for ValenzaBio and Crinetics. P.T., P.V., and W.L.M.: Employees of Immunovant, Inc. R.S.D.: Consultant for Horizon Therapeutics, Viridian Therapeutics, and ValenzaBio. The other authors have no conflicts to report.

Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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2.1.2 A Novel Monoclonal Antibody Degrades the Thyrotropin Receptor Autoantibodies in Graves' Disease

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Summary:
In this exploratory, placebo-controlled trial, patients with autoimmune thyroid disease (AITD) were randomly assigned to receive either a novel mAb that inhibits the FcRn or placebo for 12 weeks. The classification system of the medical dictionary for regulatory activities (MedDRA) was used to record AE and side effects (SE). Severity and drug relatedness were assessed according to the current guidelines of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH). Safety relevant serological parameters were measured at baseline and follow-up.

Most AE were graded as mild or moderate, with no injection site reactions reported. Drug-related SE included nervous system, gastrointestinal, and psychiatric disorders. Two SAE occurred: dysthyroid optic neuropathy (DON) and suspected autoimmune encephalomyelitis. Neither was related to the treatment.

Serum albumin concentrations decreased significantly under mAb treatment, with differences observed across study visits. A temporary elevation of total cholesterol, LDL, and high density lipoproteins (HDL), levels was observed in the mAb group. A transient increase of alkaline phosphatase (AP) and γ-Glutamyltransferase (γGT) levels were observed. Levels of both spontaneously normalized after treatment discontinuation. In both groups no significant changes in aspartate aminotransferase (ASAT) or alanine aminotransferase (ALAT) levels were observed. The reduction of SA negatively correlated with the elevation of total cholesterol, LDL, and HDL.

Reduction of IgG levels may diminish disease severity of IgG mediated AID. The novel mAb exhibited high FcRn selectivity and minimal cytotoxicity and was well tolerated by the patients. These findings highlighting its potential clinical relevance in the management of IgG-mediated AID.

Contributions:

- Study coordination and organization
- Data reporting
- Drafting the manuscript
- Statistical data analyses
- Interpretation of results
- Critical evaluation and revision

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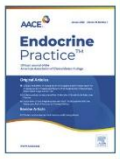

Original Article

A Novel Monoclonal Antibody Degrades the Thyrotropin Receptor Autoantibodies in Graves' Disease

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ABSTRACT

Objective: Autoantibodies against the thyrotropin receptor (TSH-R-Ab) are key mediators for the pathogenesis of Graves' disease (GD). TSH-R-Ab degradation was evaluated using several immunoassays within an exploratory, controlled trial in patients with GD receiving a monoclonal antibody (mAb) targeting the neonatal crystallizable fragment receptor (FcRn).
Methods: Serial measurements of TSH-R-Ab serum levels were performed using 3 different binding and cell-based assays in patients with GD either on medication or on placebo.
Results: In contrast to the placebo group, in which no changes were observed, a 12-week mAb therapy led to an early and significant decrease (>60%) in the serum TSH-R-Ab levels in patients with thyroidal and extrathyroidal GD, as unanimously shown in all 3 assays. These marked changes were noted already at week 7 post baseline (P <.0001 for the binding immunoassay and for the luciferase (readout) bioassay). The 3 TSH-R-Ab binding and bioassays were highly correlated in the samples of both study groups (binding immunoassay vs luciferase bioassay, r =.91, P <.001, binding vs cyclic adenosine monophosphate (cAMP) bioassay, r = 0.86, P <.001, and luciferase vs cAMP bioassay, r = 0.71, P =.006). The serological results correlated with the course of the extrathyroidal clinical parameters of GD, that is, clinical activity score and proptosis.
Conclusion: Targeting the FcRn markedly reduces the disease-specific TSH-R-Ab in patients with GD. The novel and rapid TSH-R-Ab bioassay improves diagnosis and management of patients with GD.
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Introduction

Thyroid hormone synthesis is controlled by thyrotropin (TSH), which acts at the thyrotropin receptor (TSH-R). Autoantibody mimicry of hormone action at the TSH-R and aberrant signaling of TSH-R by autoantibodies (TSH-R-Ab) cause Graves' disease (GD, hyperthyroidism) and hypothyroidism, both of which affect millions of patients worldwide.[1,2] Stimulatory TSH-R-Ab, through activation of the G-protein-coupled TSH-R, cause autoimmune hyperthyroidism and are the disease-specific serological biomarkers of GD.[3-5] TSH-R-Ab extensively activate TSH-R in both the thyroid gland and extrathyroidal TSH-R expressing target cells, for example, orbital fibroblasts, inducing the clinical signs and symptoms of GD and associated orbitopathy (GO). The TSH-R-Ab correlate with the duration, clinical activity, and severity of both GD and GO and are robust and valid predictive and prognostic factors for the course of the disease and the response to specific treatments.[4-6] TSH-R-Ab are functional and can be divided into either stimulating (TSAb), blocking (TBAb), or neutral (TNAb), according to their effect on the G-protein coupled TSH-R.[6-10] Conventional TSH-R-Ab binding assays are widely distributed and

Abbreviations: ATD, thionamide antithyroid drug; cAMP, cyclic adenosine monophosphate; CHO-MC4, chimeric Chinese hamster ovarian cells; CI, confidence interval; Fc, crystallizable fragment; FcRn, neonatal crystallizable fragment receptor; FcγR, crystallizable fragment receptor superfamily; FT3, free triiodothyronine; FT4, free thyroxine; GD, Graves' disease; GO, Graves' disease-associated orbitopathy; GS, glow sensor; ICH 6, Guidelines for Good Clinical Practice; Ig, immunoglobulin; IgG, immunoglobulin subtype G; M22-RU, ruthenium-labelled M22; MHC I, major histocompatibility complex I; OR, odds ratio; RLU, relative light units; SRR, specimen-to-reference ratio; TBAb, thyrotropin receptor blocking antibodies; TBII, thyrotropin receptor binding inhibiting immunoglobulin; TNAb, thyrotropin receptor neutral antibodies; TSAb, thyrotropin receptor stimulating antibodies; TSI, thyroid stimulating immunoglobulin; TSH, thyrotropin; TSH-R, thyrotropin receptor; TSH-R-Ab, autoantibodies against the thyrotropin receptor; Turbo TSAb, thyrotropin receptor stimulating antibodies, determined with the novel rapid bioassay; β2m, β2 microglobulin.

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are routinely used for both diagnosis and differential diagnosis of patients with GD or GO, as well as for monitoring the treatment progress. However, they are only able to determine the binding of the TSH-R-Ab, present in the serum of the patient, to the offered antigen on the platform of the immunoassay. These TSH-R binding inhibiting immunoglobulin (TBII) assays do not discriminate the antibody functionality. In contrast, specific and sensitive cell-based bioassays exclusively differentiate between the TSH-R-Ab characteristics and discriminate antibody functionality.[4,11-14]

TSH-R-Ab belong to the immunoglobulin (Ig) subtype G (IgG).[15,16] Of the Igs, the IgG subgroup has the longest half-life of approximately 21 days. The extended half-life of IgG is due to its highly effective recycling mechanism. The key enzyme for this mechanism is the neonatal crystallizable fragment receptor (FcRn).[17-20] FcRn is a widely expressed receptor, which can be found in different cell types and several tissues. The most important factor underlying the recycling mechanism is the expression of the FcRn in epithelial and endothelial cells.[19-22] FcRn is located within early endosomes inside the cells. Igs and other soluble, extracellular structures are internalized by spontaneous pinocytosis and translocated to the early endosomes. After acidification of the endosomal lumen, FcRn binds to IgG. Unbound structures are then translocated to the lysosome and degraded. The FcRn-IgG complex translocates back to the surface of the cell, where the connection between the FcRn molecules and IgG dissolves spontaneously, due to the neutral pH condition.[19,20,23-25]

In this exploratory study, we aimed to demonstrate the effect of a novel monoclonal antibody (mAb), targeting the FcRn, on the serum concentration of the disease-specific and pathogenic TSH-R-Ab in patients with autoimmune thyroid disease (GD/GO), who participated in a randomized, placebo-controlled trial. To describe the marked decrease in the serological biomarker, we serially measured these autoantibodies during and after treatment with 3 different TSH-R-Ab binding and cell-based assays, including a recently introduced novel, ultrarapid ('Turbo') cyclic adenosine monophosphate (cAMP) bioassay.

Highlights

- A novel monoclonal antibody degrades the pathogenic, disease-specific autoantibodies against the thyrotropin receptor (TSH-R-Ab)
- Herein, a novel, supersensitive, rapid TSH-R-Ab cell-based bioassay is introduced
- This novel bioassay shows high correlation with 2 other TSH-R-Ab assays as well as with clinical parameters

Clinical Relevance

Targeting the neonatal crystallizable fragment receptor markedly decreases disease-specific autoantibodies (eg, thyrotropin receptor antibodies, TSH-R-Ab) in immunoglobulin G-mediated autoimmune disorders. Accurate and rapid measurement of these specific antibodies demonstrates the clinical utility of this novel and ultrasensitive TSH-R-Ab bioassay.

Methods

Quantification of TSH-R-Ab

TSH-R Binding Inhibiting Immunoglobulin Determination

Serum TBII activity was measured with a conventional, competitive binding immunoassay according to the manufacturer's instructions (Cobas, Roche). Briefly, TSH-R-Ab in patient sera compete with the ruthenium-labeled mAb M22 (M22-Ru) for interacting with a complex, composed of a recombinant human TSH-R and a TSH-R-biotinylated Ab. After incubation for a short period, the M22-Ru-TSH-R-complex binds to streptavidin-coated microparticles and is measured using electrochemiluminescence signals. The cutoff for the conventional binding assay is 1.75 IU/L.[3,5,6]

Cell-based TSH-R Stimulating Antibody Bioassay (Thyretain TSAb)

The serum TSAb activity was measured with a chimeric TSH-R bioassay (Thyretain bioassay, QuidelOrtho Corp) according to the manufacturer's instructions. Briefly, chimeric Chinese hamster ovarian (CHO-Mc4) cells (6.7×10^4 cells/well) were taken in a frozen vial and were seeded and grown to a confluent cell monolayer in 96-well plates for 15 to 18 hours at 37.8 °C and under 5% CO_2. The cells were genetically engineered, expressing a luciferase reporter gene under the control of a cyclic adenosine monophosphate (cAMP)-dependent promoter. Serum samples, reference standards, and positive and negative controls were diluted 1:11 in reaction buffer and added to the cell monolayers, and each plate was incubated for 3 hours at 37.8 °C under 5% CO_2. TSAb in patient sera increase the intracellular cAMP level, leading to the transcription and translation of the luciferase enzyme. After a 3-hour incubation, a luciferase substrate was added, which leads to light output. Subsequently, the CHO-Mc4 cells were lysed and the relative light units (RLU) were quantified using a luminometer (Tecan Infinite M200). The cutoff for the Thyretain TSAb bioassay is 140% specimen to reference ratio (SRR).[26]

Turbo TSH-R Stimulating Antibody Bioassay

Turbo TSAb (or thyroid stimulating immunoglobulin, TSI) activity was measured with a novel, ultrarapid, sensitive, chimeric TSH-R bioassay (Turbo TSI bioassay, QuidelOrtho Corp) according to the manufacturer's instructions.[27] Briefly, patient sera, reference standards, and positive and negative controls were added to a white 96-well plate. Glow sensor (GS) luciferase-CHO-MC4 cells and a luciferase substrate were added into each well. The GS luciferase reporter had been transfected into the CHO cells via an engineered plasmid, resulting in a permanent, stimulation-independent transcription and translation of the GS. TSAb present in the samples will increase the intracellular cAMP level through the antibody and TSH-R interaction. Upon binding of cAMP, the GS reporter produces increased visible light output, which is measured as RLU using a luminometer (GloMax Discover; Promega). RLU were converted into IU/L using the standard curve. The cutoff for the Turbo TSAb assay is 0.024 IU/L.[27,28]

Study Design

The clinical trial has been approved by the local Independent Ethics Committee and performed according to the declaration of Helsinki and the Guidelines for Good Clinical Practice (ICH 6) (Kahaly G. *J Clin Endocrinol Metab*. 2023).[29] All patients at our institution have given their written informed consent prior to screening for eligibility. Patients with GD and GO randomly received either a mAb targeting the FcRn (Group A) or a placebo (Group B) for 12 weeks. Patients in group A received one of 3 different doses of the mAb. All 3 active arms were combined into one cohort for comparison against placebo. For quantification of the disease-specific TSH-R-Ab, serum samples from the locally enrolled patients were collected predose at each visit during the treatment phase, as well as during an 8-week follow-up. This manuscript is a presentation of data from a single center of a multicenter study. The

Table
Demographic, Clinical, Serological, and Biochemical Data

	Group A [n = 19]	Group B [n = 12]	P Value
Gender, n (%)			
Female	**13** (68.42)	**9** (75)	>.9999
Male	**6** (31.58)	**3** (25)	
Age (y), mean ± standard deviation (SD)	**48.65** (±11.02)	**48.08** (±12.04)	.8971
Weight, kg, mean (SD)	**78.15** (±15.22)	**70.90** (±13.44)	.0438 (*)
Height, m, mean (SD)	**1.73** (±0.06)	**1.68** (±0.11)	.1541
Smoking habits			
Nonsmoker, n (%)	**15** (78.95)	**10** (83.33)	>.9999
Smoker, n (%)	**4** (21.05)	**2** (16.67)	
Thyroidal diagnosis			
Graves' disease, n (%)	**19** (100)	**12** (100)	>.9999
Thyroid medication			
No treatment, n (%)	**7** (36.84)	**0**	.0361 (*)
Treatment, n (%)	**12** (63.16)	**12** (100)	
Antithyroid thionamide drug (ATD), n (%)	**7** (36.84)	**9** (75)	.6668
Thyroid hormone substitution, n (%)	**5** (26.32)	**3** (25)	
Mean (SD) dose of ATD, mg	**4.87** (±8.68)	**4.96** (±4.16)	.1960
Mean (SD) dose of levothyroxine, µg	**36.16** (±65.16)	**25.00** (± 46.47)	.7220
Serology			
Baseline mean (SD) serum TSH [0.55-4.78 mIU/L]	**1.50** (±1.77)	**4.88** (±6.31)	.0669
Baseline mean (SD) serum free T3 [3.5-6.5 pmol/L]	**5.49** (±1.89)	**4.96** (±0.69)	.7682
Baseline mean (SD) serum free T4 [11.5-22.7 pmol/L]	**16.64** (±5.95)	**14.29** (±4.23)	.6700
Baseline mean (SD) serum TBII [<1.75 IU/L]	**13.67** (±13.58)	**13.41** (±12.12)	.8028
Baseline serum Turbo TSAb [<0.024 IU/L]	**3.012** (±4.712)	**2.366** (±3.131)	.9608
Baseline serum Thyretain TSAb [<140 %SRR]	**878.3** (±281.1)	**868.8** (±248.2)	.5288
Graves' orbitopathy			
Severity: moderate-to-severe, n (%)	**19** (100)	**12** (100)	>.9999
Mean (SD) duration, mo	**4.37** (±2.34)	**5.25** (±2.14)	.2997
Mean (SD) clinical activity score	**5.05** (±1.08)	**5.08** (±1.17)	>.9999
Proptosis, mm, mean (SD)	**22.16** (±4.05)	**22.42** (±2.94)	.8384

Abbreviations: SRR = specimen-to-reference ratio, TBII = thyrotropin receptor binding inhibiting immunoglobulin, TSAb = thyrotropin receptor stimulating antibodies, and Turbo TSAb = thyrotropin receptor stimulating antibodies, determined with the novel bioassay.
* Significantly different (P =.01 to.05),

analyses are exploratory and not the prospectively defined end points of the main study.

Statistical Analysis

All analyses were completed with the statistical software *GraphPad Prism* (Version 9.3, GraphPad Software Inc). Each analysis was performed with a type I error of 0.05 ($\alpha = 0.05$) and a 95% confidence interval (95% CI). The baseline odds ratio (OR) between the 2 groups was calculated with a 95% CI, using the Fisher exact test. Obtained data from baseline, week 7, week 13 (end of treatment), and week 20 (end of follow-up) were tested for normality distribution, using the Shapiro-Wilk test. Normally distributed values were analyzed using parametric tests (1-way ANOVA or t test). A nonparametric test was performed (Kruskal-Wallis test or Mann-Whitney U test) if the obtained values were not normally distributed.

Results

Demographic Data

Complete demographic, clinical, and serological data are provided in the Table. With very few exceptions (eg, weight), no significant differences between both study groups were noted at the baseline.

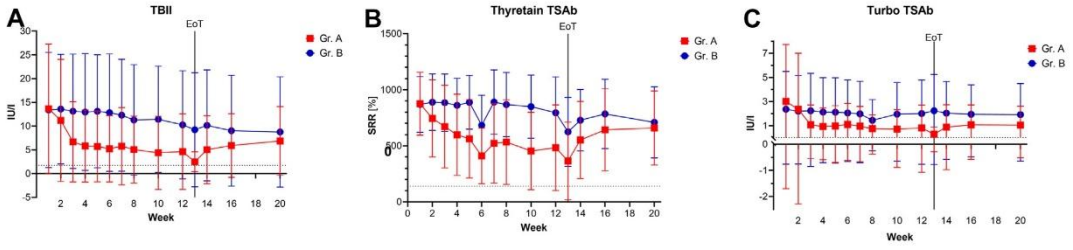

Fig. 1. Course of the TSH-R-Ab serum levels in the 2 study groups measured with the 3 assays. *A*, The cutoff for the conventional binding assay is 1.75 IU/L (dotted line). *B*, The cutoff for the cell-based bioassay is at 140% SRR (dotted line). *C*, The cutoff for the novel, ultrarapid cell-based bioassay is 0.024 IU/L (dotted line). *EoT* = end of treatment, *Gr* = group, *SRR* = specimen-to-reference ratio, *TBII* = thyrotropin receptor binding inhibiting immunoglobulin, *TSAb* = thyrotropin receptor stimulating antibodies, *Turbo TSAb* = thyrotropin receptor stimulating antibodies, determined with the novel bioassay.

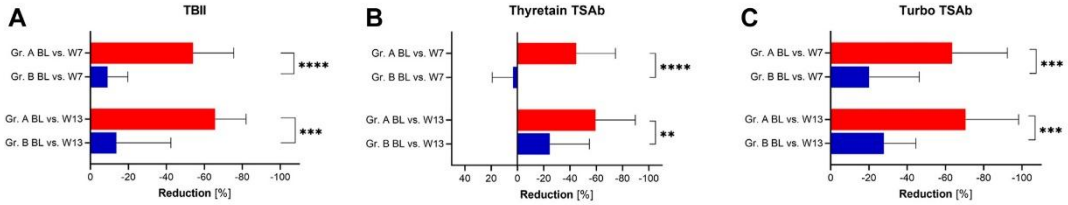

Fig. 2. Decrease of the TSH-R-Ab serum levels at weeks 7 and 13 post baseline measured with the 3 assays in the 2 study groups. ****P <.0001, ***P =.0001 to.001, **P =.001 to.01. *BL* = baseline, *Gr* = group, *SRR* = specimen-to-reference ratio, *TBII* = thyrotropin receptor binding inhibiting immunoglobulin, *TSAb* = thyrotropin receptor stimulating antibodies, *Turbo TSAb* = thyrotropin receptor stimulating antibodies, determined with the novel bioassay.

TSH-R-Ab Serum Levels

In contrast to the placebo group (study group B), in which no changes were observed (Fig. 1), all 3 TSH-R-Ab assays showed a rapid, marked, and significant decrease in the serum TSH-R-Ab levels in patients of the medication group A, already at week 7 after baseline (P <.0001 for the binding TBII and for the Thyretain bioassay with luciferase release as readout). This major decline in

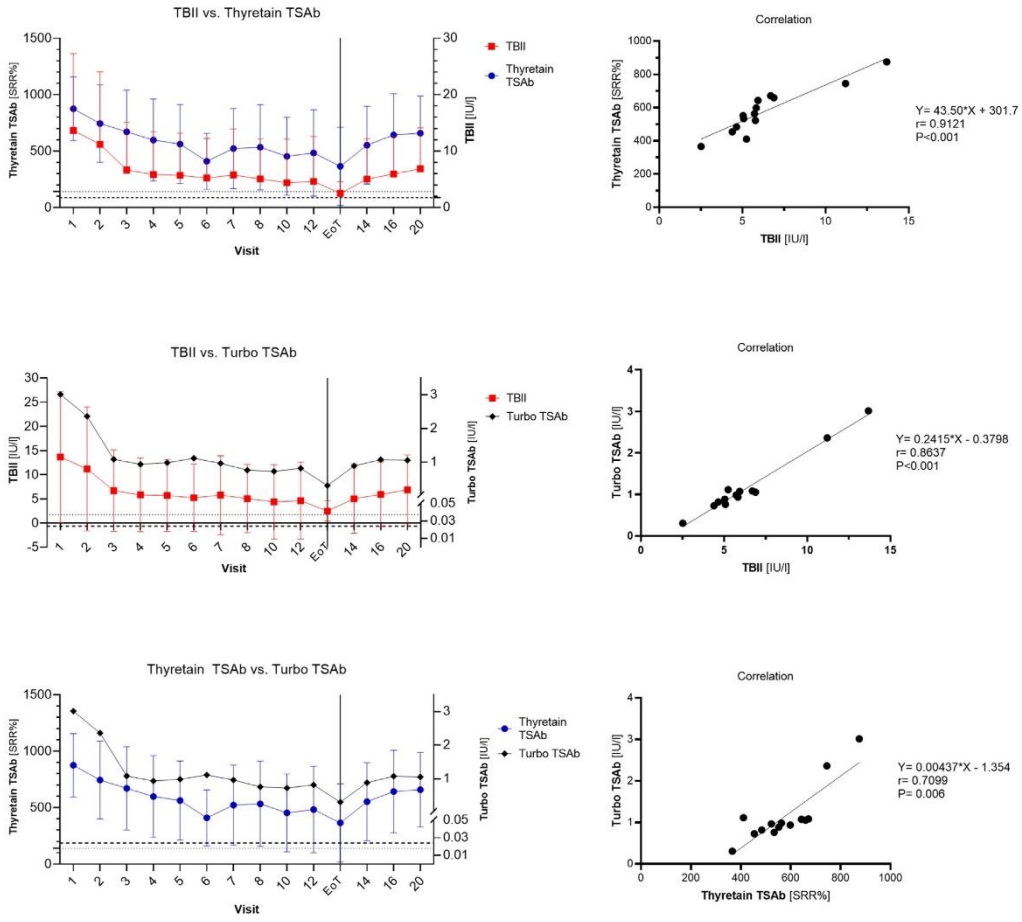

Fig. 3. One-to-one correlations of the 3 TSH-R-Ab assays. *A*, The cutoff for the conventional binding assay is at 1.75 IU/L (dotted line); the cutoff for the cell-based bioassay is at 140% SRR (dashed line). *B*, The cutoff for the conventional binding assay is 1.75 IU/L (dotted line); the cutoff for the novel, ultrarapid cell-based bioassay is 0.024 IU/L (dashed line). *C*, the cutoff for the novel, ultrarapid cell-based bioassay is 0.024 IU/L (dotted line). The cutoff for the cell-based bioassay is 140% SRR (dashed line). *EoT* = end of treatment, *r* = coefficient of correlation, *SRR* = specimen-to-reference ratio, *TBII* = thyrotropin receptor binding inhibiting immunoglobulin, *TSAb* = thyrotropin receptor stimulating antibodies, *Turbo TSAb* = thyrotropin receptor stimulating antibodies, determined with the novel bioassay.

the TSH-R-Ab serum concentration in group A sustained with a nadir, 12 weeks post baseline (week 13, Fig. 2). After discontinuation of treatment, the serum TSH-R-Ab levels returned to the approximate baseline levels.

Assay Correlations

The 3 TSH-R-Ab binding and bioassays show high correlation (2-tailed Spearman test) for the samples of group A (Fig. 3). Most specifically, the recently introduced ultrarapid, cell-based Turbo TSI bioassay, with cAMP release as readout, strongly correlated with both conventional binding immunoassay (P <.001) and Thyretain bioassay (P =.006).

TSH-R-Ab Reduction and Clinical Correlation

Two examples are offered: a patient receiving the mAb medication (group A, Fig. 4) and a patient on placebo (group B, Fig. 5). Patient A (group A) was a naïve, untreated patient with GD and GO. The Turbo TSAb and TBII serum levels declined already after the first administration and reached a nadir after the third mAb administration. The TBII serum concentration lowered beneath the cutoff (<1.75 IU/L) and remained negative. In comparison, the Turbo TSAb serum levels remained low positive during further treatment and the subsequent follow-up period. The patient was biochemically euthyroid with thyroid-related hormone serum levels (TSH, free thyroxine, FT4, and free triiodothyronine, FT3) within the normal range. Thyretain TSAb declined until week thirteen. The initial clinical activity score (CAS) of GO declined after 2 subcutaneous mAb administrations from 6 to 3 and was further reduced to 1, after 7 mAb administrations. Another relevant parameter of GO, proptosis, declined from 22 mm at the baseline to 18 mm after 5 mAb administrations. Proptosis remained constant (18 mm) during further treatment and follow-up observation. Of the 3 TSH-R-Ab assays, the novel Turbo TSI bioassay correlated best with clinical activity and severity of the disease. In detail, Turbo TSAb, Thyretain TSAb, and TBII strongly and significantly correlated (Fig. 4, 2-tailed Spearman test) with CAS (r = 0.9027, P <.001; r = 0.7192, P =.007; and r = 0.644, P =.020; respectively), as well as with proptosis (r = 0.8692, P <.001; r = 0.8598, P <.001, and r = 0.7667, P =.004; respectively).

In contrast, on placebo (group B), the TSH-R-Ab serum levels measured with the 2 bioassays remained practically unchanged, while the TBII serum levels increased during the first 7 weeks. Clinically, proptosis remained unchanged during the complete observation period, whereas a moderate improvement in CAS was noted on placebo, and there was no correlation between the TBII, Turbo, and Thyretain TSH-R-Ab results and CAS: r = −0.0175, P =.974; r = 0.1048, P =.731; and r = −0.0175, P =.987, respectively. Due to the unchanged proptosis value, no correlations could be evaluated between the clinical severity of GO and the serology markers.

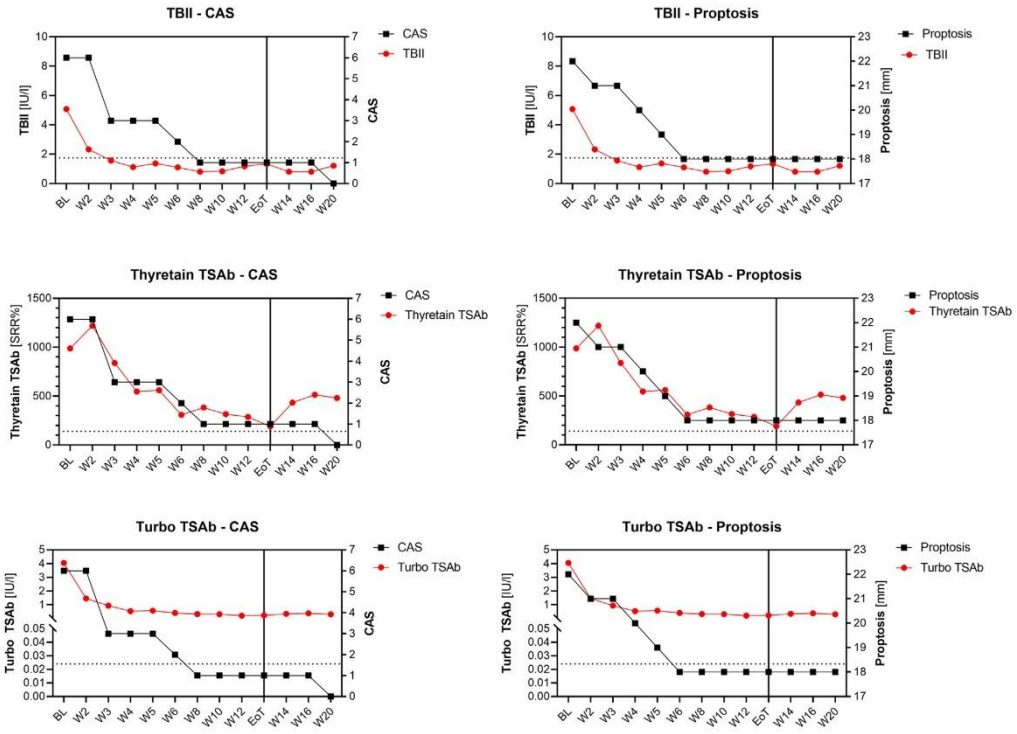

Fig. 4. Correlation of serology & phenotype in a patient receiving the medication. *CAS* = clinical activity score, *EoT* = end of treatment, *SRR* = specimen-to-reference ratio, *TBII* = thyrotropin receptor binding inhibiting immunoglobulin, *TSAb* = thyrotropin receptor stimulating antibodies, *Turbo TSAb* = thyrotropin receptor stimulating antibodies, determined with the novel bioassay. Cutoff values for the TBII, Turbo TSAb, and Thyretain TSAb assays (<1.75 IU/L, <0.024 IU/L, and <140% SRR; respectively) have been marked with dotted lines.

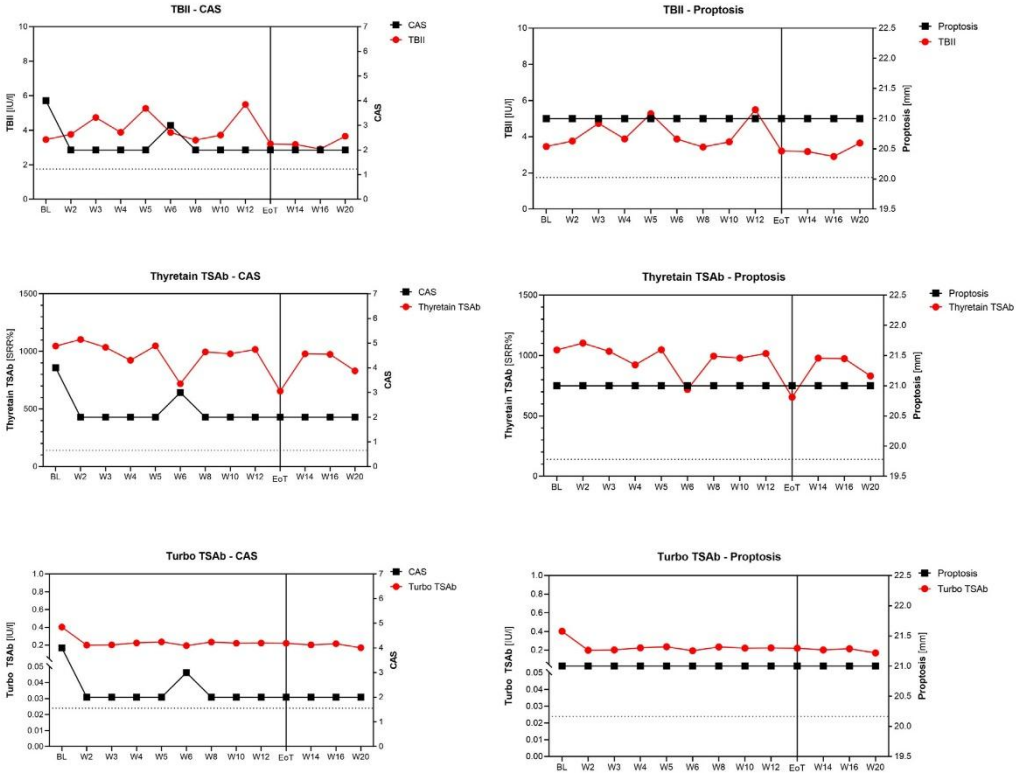

Fig. 5. Correlation of serology and phenotype in a patient on placebo. *CAS* = clinical activity score, *EoT* = end of treatment, *SRR* = specimen-to-reference ratio, *TBII* = thyrotropin receptor binding inhibiting immunoglobulin, *TSAb* = thyrotropin receptor stimulating antibodies, *Turbo TSAb* = thyrotropin receptor stimulating antibodies, determined with the novel bioassay. Cutoff values for the TBII, Turbo TSAb, and Thyretain TSAb assays (<1.75 IU/L, <0.024 IU/L, and <140% SRR; respectively) have been marked with dotted lines.

Discussion

The primary objective of this exploratory study was to assess the change over time in serological biomarkers with 3 different TSH-R-Ab binding and cell-based assays (including assay correlation) that were associated with administration of an investigational agent. An additional objective was to assess the correlation between changes in biomarkers and any treatment-related change in clinical outcome.

This manuscript illustrates the marked effect of a novel monoclonal antibody, targeting the FcRn, on the serum concentration of the pathogenic, disease-specific immunoglobulin TSH-R-Ab in patients with autoimmune thyroid disease. During a 12-week treatment phase, a reduction of approximately 60% of the TSH-R-Ab titer was registered with variability in IgG reduction seen between the different dose groups. The TSH-R-Ab are acknowledged as the specific and sensitive biomarkers of the T helper type 2, humoral immunity-induced Graves' disease. Hence, lowering the serum concentration of these pathogenic antibodies will relieve the thyrocytes from permanent stimulation and cell activation to produce thyroid hormones. As these antibodies circulate in the peripheral blood and bind to various target cells expressing the TSH-R, for example, orbital and/or skin pretibial fibroblasts, lowering the serum levels of TSH-R-Ab will decrease the activation and inflammation of the orbital cells, thus markedly limiting the release of both proinflammatory cytokines and hydrophilic mucopolysaccharides causing local edema and tissue expansion.

To demonstrate this significant and clinically relevant effect, we have used a widely distributed conventional TSH-R-Ab binding immunoassay as well as 2 sensitive cell-based bioassays. More specifically, we are introducing an ultrarapid, supersensitive bioassay with cAMP as readout and a very low cutoff of 0.024 IU/L. All 3 TSH-R-Ab highly correlated pertaining to the serological results as well as with the clinical parameters. This novel and rapid bioassay uses a novel cAMP biosensor (glow sensor). The glow sensor is an engineered form of firefly luciferase in which the cAMP-binding domain of protein kinase A is fused between the N- and C-termini such that the luciferase is inactive until cAMP binds to the cAMP binding site. Using this biosensor, the luciferase activity is proportional to the intracellular cAMP levels.[30] A TSAb bioassay (Turbo TSI bioassay) was generated using a CHO-K1 stable cell line that expresses both the same chimeric TSH-R (Mc4) used in the Thyretain TSAb bioassay and the cAMP-dependent biosensor.[27] The Turbo TSI bioassay allows for the detection of TSAb in serum samples at room temperature, in a real-time homogeneous format, which delivers results at 60 minutes. It does not require cell culture, sample dilution, washing, or cell lysis steps.

The novel, fully human anti-FcRn mAb has been selected by its high binding affinity to the FcRn. Further, the crystallizable fragment has been engineered, reducing effector functions, that is, antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity. The mAb competes with the pathogenic TSH-R-Ab for interaction with the FcRn. Due to the high

affinity, more TSH-R-Ab remain unbound to the receptor and are degraded in the lysosome. Furthermore, the interventional monoclonal antibody remains bound to the FcRn after translocation to the surface membrane, leading to prolonged inhibition of the receptor. So far, this novel mAb has been tested in phase 1 and 2 clinical trials for myasthenia gravis, warm autoimmune hemolytic anemia, and autoimmune thyroid disease, showing a marked decrease in the disease-related autoantibodies.[29,31-33] Currently, it is under clinical evaluation in phase 2 and 3 trials for generalized myasthenia gravis, chronic inflammatory demyelinating polyneuropathy, and GO.[34-36]

Several limitations of the present exploratory work should be discussed: (a) the nonprospective nature of the study, b) all 3 active treatment arms were combined in comparison with placebo, c) the relatively small total number of treated and evaluated patients; with a higher number of included patients, statistical power usually increases while potential bias will decrease, (d) measurements of the TSH-R-Ab have been performed with different lots, potentially resulting in a small but noticeable oscillation of the obtained results, (e) clinical evaluation of the CAS and proptosis have been performed by 2 experts; however, an investigator-dependent bias cannot be excluded, (f) statistical analyses were neither prospectively defined nor controlled for multiplicity, and g) different mAb dosing groups had varying degrees of IgG and TSH-R-Ab reduction that may have actually made our findings more challenging to uncover.

In conclusion, we have tested the efficacy of a novel, anti-FcRn monoclonal antibody that degrades the pathogenic immunoglobulins and markedly reduces the serum concentration of the disease-specific TSH-R-Ab with the help of 3 different assays. This therapeutically alternative approach is of interest for both Graves' thyroidal and extrathyroidal diseases. In addition, a newly introduced rapid and very sensitive cell-based bioassay highly correlated with older, wildly distributed, and established TSH-R-Ab assays. This useful TurboTSI bioassay correlated the best with the clinical activity and severity parameters of autoimmune thyroid disease.

Disclosure

The JGU Medical Center receives research-associated funding from Quidelortho, San Diego, CA, USA, and from Immunovant Inc., New York City, NY, USA. G.J.K. consults for Immunovant and QuidelOrtho.

Author contributions

J.W. and S.A. contributed equally to this manuscript and share first authorship. J.W. and G.J.K. wrote and revised the manuscript, S.A. performed all TSH-R-Ab measurements, J.W. drafted the figures, and I.K. and G.J.K. critically reviewed and edited the manuscript.

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2.1.3 Safety and tolerability of anti-FcRn monoclonal antibody in thyroid autoimmunity

Published in: *Exploration of Immunology*, 2024;4:341–57

Summary:
In this exploratory, placebo-controlled trial, patients with autoimmune thyroid disease were randomly assigned to receive either the novel mAb antibody against the FcRn or placebo for 12 weeks. AE and SE were documented using MedDRA classification. Severity was categorized based on interference with daily activities and assessed for drug relatedness according to the ICH guidelines. Safety relevant serological parameters were measured at baseline and follow-up.

Most AE were mild or moderate, with no injection site reactions reported. Drug-related SE included nervous system, gastrointestinal, and psychiatric disorders. Two SAE occurred-dysthyroid optic neuropathy and suspected autoimmune encephalomyelitis-but neither was attributed to the drug.

Serum albumin concentrations decreased significantly under mAb treatment, with differences observed across study visits. Total cholesterol, LDL, and HDL levels increased during mAb treatment but returned to baseline post-therapy, with no significant differences in triglyceride levels between groups. AP levels temporarily increased but normalized after treatment, with no significant changes in ASAT or ALAT levels. γGT levels showed transient elevations that resolved post-treatment. SA reduction was negatively correlated with cholesterol levels, whereas positive correlations were observed between AP and γGT in both groups.

Reducing IgG levels may alleviate disease severity in AID given FcRn's role in IgG homeostasis and immune defense. The novel mAb exhibited high FcRn selectivity and minimal cytotoxicity. The findings of this study support its safety and tolerability, highlighting its potential clinical relevance in the management of IgG-mediated AID.

Contributions:

- Study coordination and organization
- Data reporting
- Drafting the manuscript
- Statistical data analyses
- Interpretation of results
- Critical evaluation and revision

Exploration of Immunology

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Safety and tolerability of anti-FcRn monoclonal antibody in thyroid autoimmunity

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Abstract

Aim: The clinical symptoms of autoantibody (AAb)-mediated autoimmune diseases (AID) usually correlate with the AAb-titer. Immunoglobulins (Igs) of the IgG type are actively recycled by the neonatal crystallizable fragment receptor (FcRn). The most common Ig type of AAb is IgG. This explorative study evaluates the safety and tolerability of a fully human anti-FcRn monoclonal antibody (mAb) in patients with thyroid autoimmunity (TA).

Methods: Adverse events (AEs) and serious AEs (SAEs) were documented and coded according to the standardized Medical Dictionary for Regulatory Activities (MedDRA). AEs were followed up, and seriousness, as defined by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)-guideline E6, was documented. All AEs were analyzed for a possible underlying cause, and if not identified, were graded as side effects (SEs). Additionally, safety-relevant serological parameters (liver function and blood cell counts) were evaluated. Furthermore, laboratory parameters influenced by other anti-FcRn agents in clinical studies were considered.

Results: Of 31 patients with TA, 19 were administered the anti-FcRn mAb subcutaneously once weekly for 12 weeks, while 12 were on placebo. Compared to placebo, there was no increased occurrence of AE and/or SE in the mAb group. mAb treatment increased total, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) cholesterol. A mAb treatment-induced transient decrease in serum albumin strongly correlated with an increase in total cholesterol (r = –0.893, P = 0.012). Overall compared to placebo, there were no significant changes in blood cell counts, complement factors, or liver enzymes. Serological changes were transient and spontaneously normalized after treatment completion. Two SAEs were deemed no-drug induced (dysthyroid optic neuropathy and a post-COVID infection associated autoimmune encephalomyelitis).

Conclusions: The anti-FcRn mAb is a safe and well-tolerated therapy for AAb-mediated AID.

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Keywords

Anti-FcRn monoclonal antibody, drug safety, adverse events, side effects, thyroid autoimmunity

Introduction

The half-life of immunoglobulin (Ig) G and human serum albumin (HSA) is approximately 21 days, with IgG being the most common Ig in circulation [1–3]. The relevant half-life is due to a specific receptor-mediated recycling mechanism. The neonatal crystallizable fragment receptor (FcRn) was first described in 1964 [4]. FcRn is a major histocompatibility complex I (MHC-I)-like heterodimer consisting of a non-covalently linked α and β2m subunit. The presence and function of FcRn have been extensively characterized over the past decades [5–8]. Three essential functions of FcRn have been described: (a) transport of IgG across membrane barriers, (b) uptake and presentation of IgG-bound antigens to immune cells, and (c) protection of IgG and albumin from excessive degradation (recycling loop). FcRn's specificity for its ligands is high; no other Igs or proteins bind to the receptor. The transport and recycling mechanisms are strictly pH-dependent [9–11]. By extending the half-life of IgG, FcRn contributes to maintaining immune defense in healthy organisms and significantly impacts the onset and course of autoimmune diseases (AID). The severity of IgG-mediated AID, such as thyroid autoimmunity (TA) or myasthenia gravis (MG), strongly correlates with the titer of pertaining autoantibodies (AAb) [12–16]. The receptor-mediated recycling loop of AAb can significantly influence the onset and progression of AAb-mediated AID. For IgG-mediated AID, e.g., TA, currently only unspecific and symptomatic treatment is available [17, 18]. In contrast to disease-targeted therapy, non-specific treatments often cause side effects (SEs). As early as the 1990s, it was shown that mice administered AAb developed AID. Knock-out animals with an FcRn deficiency did not develop AID or a milder form [19–21]. This led to considering FcRn as a potential target for treating AAb-mediated AID. In recent years, both anti-FcRn-Ab and engineered Fc targeting FcRn have been developed for the therapy of IgG-mediated AID [22–28]. However, the use of anti-FcRn-Ab in patients with TA was reported in one single study only [29, 30].

Hence, this exploratory monocentral study evaluates the safety of a novel anti-FcRn monoclonal antibody (mAb) in patients with TA who participated in a randomized, placebo-controlled trial [29, 30]. The mAb binds with high affinity to the FcRn at acid and neutral pH. Further, the Fc has been engineered, reducing effector functions, that is, antibody-dependent cell-mediated cytotoxicity and complement-dependent cytotoxicity.

Materials and methods

Study design and criteria of eligibility

The clinical trial has been approved by the local independent Ethics Committee (IEC) of Rhineland Palatinate (IEC no. 2019-14297-AMG; approved March 11, 2020) and performed according to the Declaration of Helsinki and the Guidelines for Good Clinical Practice (GCP). All patients have given their written informed consent prior to screening for eligibility. Patients with TA randomly received either the anti-FcRn mAb (treatment group) or placebo for 12 weeks. This manuscript is a presentation of data from a single center. The analyses are exploratory and do not include the prospectively defined endpoints of the main multicenter trial [29].

Patients aged 18 years and older were considered eligible for participation if they had active TA within nine months of screening, euthyroidism or mild thyroid dysfunction at baseline, and were on a stable medical regimen. Exclusion criteria included prior treatment with steroids within three weeks prior to screening or other immunosuppressive medications within the past nine months before baseline. Patients with acute or chronic viral hepatitis, relevant malignancies, or chronic renal failure were excluded. Patients with IgG levels < 6 g/L, serum albumin levels < 3.5 g/L, absolute neutrophil counts < 1,500 cells/mm^3, or elevated (> 1.5-fold) liver enzymes at screening did not meet eligibility criteria. A comprehensive list of inclusion and exclusion criteria is available in the Supplementary material.

Documentation of adverse events and SEs

All recorded adverse events (AEs) were assigned codes using the Medical Dictionary for Regulatory Activities (MedDRA). MedDRA is a medical terminology developed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). The use of MedDRA is strongly recommended to accurately and transparently describe the safety profile and quantify potential AE and SEs during drug therapy or clinical trials. The English version 24.1 of MedDRA was utilized, and the relevant guidelines were followed. The severity of all AE was assessed and categorized as mild, moderate, or severe, as follows: mild (no interference with daily activities), moderate (interference with daily activities), and severe (prevention of daily activities). Follow-up was conducted for all AE, and the final outcome was documented. Each AE was evaluated for its relationship to drug intake and seriousness, based on the criteria outlined in the ICH guideline-E6 for GCP.

Demographic and clinical data

Forty patients have been screened for eligibility. Of the 31 randomized patients, 19 received the mAb and 12 placebo. Of the remaining nine, six patients were excluded because they did not meet the inclusion criteria, while three patients were not randomized due to the early termination of the trial. One patient in the treatment group withdrew from the study after week four. Complete demographic, clinical, and serological data are offered in Table 1. With very few exceptions (e.g., weight), no significant differences were noted between the groups at baseline.

Table 1. Demographic and serological data

Study group	mAb (*n* = 19)	Placebo (*n* = 12)	*P*-value
Gender, *n* (%)			> 0.999
Female	13 (68.42)	9 (75)	
Male	6 (31.58)	3 (25)	
Age (years), mean ± SD	48.65 ± 11.02	48.08 ± 12.04	0.670
Weight (kg), mean ± SD	78.15 ± 15.22	70.90 ± 13.44	0.044 (*)
Height (m), mean ± SD	1.73 ± 0.06	1.68 ± 0.11	0.154
Smoking habits			> 0.999
Non-smoker, *n* (%)	15 (78.95)	10 (83.33)	
Smoker, *n* (%)	4 (21.05)	2 (16.67)	
Duration of thyroid autoimmunity (month), mean ± SD	4.37 ± 2.34	5.25 ± 2.14	0.269
Serology (baseline), mean ± SD			
Serum albumin (32–55 g/L)	46.74 ± 2.45	47.92 ± 2.50	0.335
Cholesterol (0–119 mg/dL)	204.10 ± 52.95	206.90 ± 33.43	0.727
HDL (< 40 mg/dL)	62.32 ± 16.27	61.58 ± 15.08	0.696
LDL (0–129 mg/dL)	123.80 ± 46.89	125.70 ± 32.11	0.712
TG (0–199 mg/dL)	90.58 ± 59.12	100.80 ± 44.05	0.174
ASAT (0–41 U/L)	17.79 ± 4.54	17.50 ± 3.26	0.944
ALAT (0–45 U/L)	18.68 ± 10.27	14.92 ± 6.63	0.263
AP (35–104 U/L)	87.11 ± 29.52	78.17 ± 18.30	0.453
γGT (0–65 U/L)	25.00 ± 26.06	15.17 ± 5.11	0.772
Lymphocytes (abs.) (1–4 × 10E9/L)	1.90 ± 0.59	2.06 ± 0.67	0.787
Monocytes (abs.) (0.1–0.9 × 10E9/L)	0.38 ± 0.22	0.35 ± 0.07	0.745
Platelets (150–350 × 10E9/L)	260.40 ± 64.28	266.80 ± 58.58	0.735
WBC (4–10.7 × 10E9/L)	6.41 ± 1.75	6.31 ± 1.55	0.897
CH50 (79–187 uEq/mL)	111.90 ± 34.07	115.80 ± 25.88	0.757
C3c (0.9–1.8 g/L)	1.16 ± 0.17	1.17 ± 0.19	0.895

* Significant difference. *n*: number of patients/events. γGT: gamma-glutamyltransferase; abs.: absolute number; ALAT: alanine aminotransferase; AP: alkaline phosphatase; ASAT: aspartate aminotransferase; C3c: complement factor 3c; CH50: complement factor CH50; HDL: high-density lipoprotein; LDL: low-density lipoprotein; mAb: monoclonal antibody; SD: standard deviation; TG: triglyceride; WBC: white blood cell

Serological parameters

The collection of serological parameters was carried out at predefined visits. This exploratory study focused on typical safety-related parameters (liver function and blood cell titers). Furthermore, parameters that were influenced by other anti-FcRn mAb or Fc in clinical trials were considered (serum albumin, complement system factors, and blood lipid levels). To evaluate a potential influence on these laboratory parameters by the mAb, the lab parameters were analyzed on day 1 (D1, baseline), D50, D78, and D134 (end of study).

Statistical analysis

All serological results obtained at the four visits (D1, D50, D78, and D134) were analyzed. The course has been plotted and the area under the curve (AUC) was calculated for each parameter. To document trends between active treatment and follow-up phases, the delta between each evaluation visit was calculated. Each parameter has been evaluated (a) within the study group and (b) between the treatment groups. Analysis was performed with a type I error of 0.05 ($\alpha = 0.05$) and a 95% confidence interval (95% CI). Obtained data were tested for statistical significance using either the Wilcoxon test or the Mann-Whitney-*U* test (group internal tests and group comparison, respectively). Parameters were tested for various correlations using Spearman's correlation test. Correlations were rated according to Cohen's criteria as minor ($0.1 < r < 0.3$), moderate ($0.3 < r < 0.5$), or high ($r > 0.5$). Analyses were performed with the statistical software GraphPad Prism (version 9.3, GraphPad Software Inc.). Furthermore, the estimated effect of the time and baseline value has been investigated using a mixed linear model (IBM SPSS Statistics, version 27, IBM Inc.) during the active treatment phase. Estimated effect for the treatment duration, considering the baseline values, analysis was performed with a type I error of 0.05, and results are presented as an estimate with 95% CI. In addition, the estimated effect of the treatment arm considering the baseline values was evaluated.

Results

Safety

A total number of 61 AEs were reported by 26 patients (83.87%) in both groups. The most frequent AEs were: nervous system disorders ($n = 22$), gastrointestinal disorders ($n = 7$), infections and infestations ($n = 7$), as well as musculoskeletal and connective tissue disorders ($n = 5$) (Table 2). The majority of the occurred AE were transient and mild or moderate (62.30% and 29.51%, respectively). No injection site AE occurred during or after mAb administration. Of the observed AE, 28/61 (45.90%) were drug-related SE: 10/23 (43.48%) and 18/38 (47.37%) in the placebo and mAb groups, respectively (Table 3). Occurred SE were: nervous system disorders (lethargy, $n = 12$), gastrointestinal disorders (diarrhea, $n = 3$; nausea, $n = 3$), general disorders and administration site conditions (ankle edema, $n = 1$; erythema, $n = 1$; limb edema, $n = 1$), infections and infestations (herpes simplex infection, $n = 2$; shingles, $n = 1$), musculoskeletal and connective tissue disorders (arthralgia, $n = 2$), and psychiatric disorders (insomnia, $n = 2$). All SEs were transient and either mild (67.86%) or moderate (32.14%).

Two serious AEs (SAEs) occurred in the treatment group. One patient reported deterioration of visual acuity at visit D78. Orbital MRI confirmed dysthyroid optic neuropathy (DON). At the time of diagnosis, the patient had received 12 out of 12 doses of the mAb. The SAE was deemed as "not drug-related". According to the European guidelines for thyroid eye disease (TED), the patient was administered intravenous glucocorticoids every second day [single dose of 0.75 g methylprednisolone (MP) per infusion, cumulative dose of 7.5 g]. Intravenous steroids led to significant clinical improvement and the patient was discharged after two weeks.

The second patient developed a SARS-CoV-2 infection at D85. Subsequently, the patient reported worsening visual acuity with visual field defects and tingling paresthesia in the hands and feet. At the onset of the COVID infection, the patient had received 11 of the foreseen 12 mAb injections. Administered oral steroids were not helpful. Orbital MRI revealed significant inflammatory lesions of the central nervous

Table 2. MedDRA-coded adverse events

Adverse event (MedDRA SOC & LLT)	Total number (*n*)	mAb (*n*)	Placebo (*n*)
Cardiac disorders	1		
Palpitations		1	
Ear and labyrinth disorders	1		
Ear noises		1	
Eye disorders	3		
Deterioration of visual acuity		2	
Optic neuropathy[#]		1	
Gastrointestinal disorders	7		
Aphthae			1
Diarrhea		1	2
Nausea		2	1
General disorders and administration site conditions	4		
Ankle edema		2	
Erythema		1	
Limb edema		1	
Infections and infestations	7		
Herpes simplex infection		1	1
Hordeolum			1
Inguinal abscess		1	
SARS-CoV-2 infection		1	
Shingles		1	
Vaginal mycosis		1	
Injury, poisoning, and procedural complications	1		
Sprain			1
Investigations	2		
Increased intraocular pressure		1	1
Musculoskeletal and connective tissue disorders	5		
Arthralgia		1	2
Groin pain		1	
Myalgia		1	
Nervous system disorders	22		
Autoimmune encephalomyelitis[#]		1	
Dizziness		1	
Headache			6
Lethargy		8	4
Paresis		1	
Paresthesia		1	
Psychiatric disorders	2		
Insomnia		1	1
Reproductive system and breast disorders	3		
Irregular menstruation		3	
Skin and subcutaneous tissue disorders	1		
Neurodermatitis			1
Vascular disorders	2		
Hypertension		1	1
Total number of adverse events		38	23
Total number of patients with adverse events (%)		15/19 (78.95)	11/12 (91.67)
Total number of patients with serious adverse events (%)		2/19 (10.52)	0/12 (0.00)

[#] Adverse event classified as serious adverse event. *n*: number of patients/events. LLT: lower limit term; mAb: monoclonal antibody; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class

Table 3. MedDRA-coded drug-related side effects

Drug-related side effect (MedDRA SOC & LLT)	Total number (*n*)	mAb (*n*)	Placebo (*n*)
Gastrointestinal disorders	6		
Diarrhea		1	2
Nausea		2	1
General disorders and administration site conditions	3		
Ankle edema		1	
Erythema		1	
Limb edema		1	
Infections and infestations	3		
Herpes simplex infection		1	1
Shingles		1	
Musculoskeletal and connective tissue disorders	2		
Arthralgia		1	1
Nervous system disorders	12		
Lethargy		8	4
Psychiatric disorders	2		
Insomnia		1	1
Total number of drug-related side effects		18	10
Total number of patients with drug-related side effects (%)		12/19 (63.16)	8/12 (66.67)
Total number of patients with serious drug-related side effects (%)		0/19 (0.00)	0/12 (0.00)

n: number of patients/events. LLT: lower limit term; mAb: monoclonal antibody; MedDRA: Medical Dictionary for Regulatory Activities; SOC: system organ class

system (CNS). A control cranial MRI confirmed the inflammatory lesions. Based on imaging and present lymphocytic pleocytosis in the cerebrospinal fluid, suspected virus-induced autoimmune encephalomyelitis was diagnosed. Hence, the SAE was deemed as "not drug-related". During hospitalization, the patient received five repetitive daily doses of 1 g intravenous MP (cumulative dose: 5 g IVMP) and underwent five sessions of plasmapheresis. Unfortunately, the patient did not respond to the above treatments. Hence, rituximab (RTX) 1 g was administered intravenously twice within two weeks, which led to clinical stabilization. However, the SAE persisted beyond the patient's last visit.

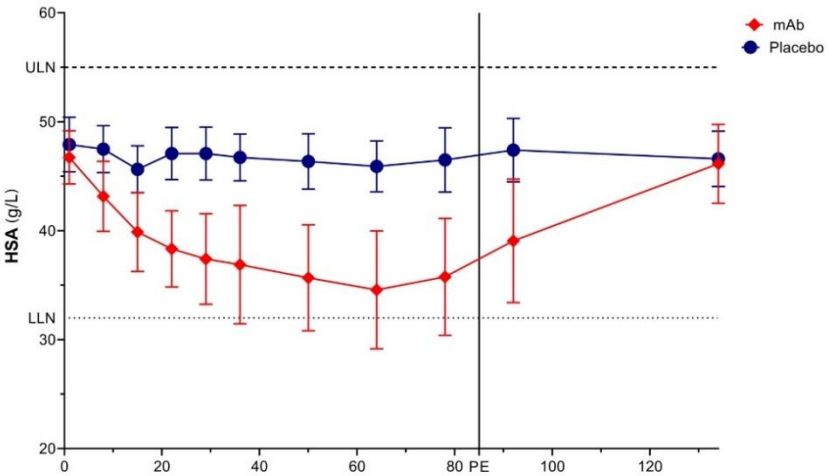
Serology

Serum albumin

On mAb, HSA decreased after the first injection, reaching a nadir at D50 (HSA_{D1} vs. HSA_{D50}, $P < 0.001$). HSA levels spontaneously normalized to approximate baseline levels at visit D134 (HSA_{D1} vs. HSA_{D134}, $P > 0.999$). The estimated effect of the treatment duration negatively impacted HSA concentration (estimate = −0.114 g/L, 95% CI: −0.153/−0.076, $P < 0.001$). While deltas between D1–D50 and D1–D78 were not different ($P > 0.999$), deltas between D1–D134 and D1–D50, as well as D1–D78, were distinct ($P = 0.014$ and $P = 0.023$, respectively). No significant differences were observed with placebo. mAb AUC [5,182 (g/L)*d, 95% CI: 4,829/5,536] was lower compared to placebo [6,228 (g/L)*d, 95% CI: 6,032/6,424] ($P < 0.001$). Considering the baseline values, the estimated effect for the treatment group, demonstrated a negative impact vs. placebo (estimate = −5.560 g/L, 95% CI: −8.566/−2.555, $P < 0.001$). Notably, the groups differed at visits D50 and D78 ($P < 0.001$ and $P < 0.001$, respectively), but no significant variance was observed at visit D134 ($P = 0.549$). Taken together, compared to placebo, mAb transiently reduced HSA with subsequent normalization at therapy completion (Figure 1).

Lipids

The analyzed blood lipid levels encompass total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and triglycerides (TGs). The anti-FcRn mAb increased serum total cholesterol concentration with a peak at D50 ($cholesterol_{D1}$ vs. $cholesterol_{D50}$, $P = 0.002$). Subsequently, these values spontaneously returned to baseline levels ($cholesterol_{D1}$ vs. $cholesterol_{D134}$, $P > 0.999$). Treatment duration



Number of patients

	D1	D8	D15	D22	D29	D36	D50	D64	D78	D92	D134
mAb	19	19	18	18	17	17	16	14	13	13	13
Placebo	12	12	11	11	11	11	11	11	10	10	10

Figure 1. Course of serum albumin. D: day; HSA: human serum albumin; LLN: lower limit of normal (32 g/L; dotted line); mAb: monoclonal antibody; PE: primary endpoint; ULN: upper limit of normal (55 g/L; dashed line)

positively affected total cholesterol (estimate = 0.830 mg/dL, 95% CI: 0.521/1.139, $P < 0.001$). Delta values between D1–D50 and D1–D78 were not different ($P = 0.568$). In contrast, values between D1–D134 and D1–D50 displayed significant variations ($P = 0.003$). On placebo, no differences in total cholesterol levels were noted between visits or delta values. The estimate for the treatment duration yielded a negative effect (estimate = –0.037 mg/dL, 95% CI: –0.277/0.203, $P = 0.758$). mAb AUC [32,364 (mg/dL)*d, 95% CI: 25,933/38,796] and placebo [28,358 (mg/dL)*d, 95% CI: 24,435/32,280] did not differ ($P = 0.334$). The estimated effect of mAb, considering baseline values, demonstrated a positive effect compared to placebo (estimate = 39.33 mg/dL, 95% CI: 20.437/58.225, $P < 0.001$). Significant differences were observed at D50 ($P = 0.004$), but not at D78 and D134 ($P = 0.181$ and $P = 0.111$).

On mAb, compared to baseline, serum LDL increased at visits D50 ($P = 0.002$) and D78 ($P = 0.014$). LDL levels spontaneously normalized to baseline values after mAb withdrawal (LDL_{D1} vs. LDL_{D134}, $P > 0.999$). The estimate for treatment duration showed a positive effect (estimate = 0.555 mg/dL, 95% CI: 0.319/0.790, $P < 0.001$). Although differences were not observed between D1–D50 and D1–D78 delta values ($P > 0.999$), differences were evident between D78–D134 and both D1–D50 ($P = 0.002$) and D1–D78 ($P = 0.005$). On placebo, no differences were observed at all visits or in the delta values. The estimate for the treatment duration revealed a negative but non-significant effect for placebo (estimate = –0.051 mg/dL, 95% CI: –0.270/0.167, $P = 0.639$). The AUC for the anti-FcRn mAb [19,243 (mg/dL)*d, 95% CI: 13,623/24,864] and placebo [16,893 (mg/dL)*d, 95% CI: 13,263/20,523] did not differ ($P = 0.521$). Notably, the estimated effect for the treatment groups concerning baseline values showed a positive effect for mAb (estimate = 23.135 mg/dL, 95% CI: 10.952/35.318, $P < 0.001$). At none of the considered visits was any registered difference between the groups. However, the calculated delta values D1–D50, D1–D78, and D78–D134 differed between the two groups ($P < 0.001$, $P = 0.017$, and $P = 0.007$, respectively).

Throughout the study, no significant differences in HDL levels were observed. The estimate for the treatment duration revealed a positive mAb effect (estimate = 0.142 mg/dL, 95% CI: 0.045/0.240, $P = 0.005$) and a negative effect for placebo (estimate = –0.065 mg/dL, 95% CI: –0.015/0.019, $P = 0.124$). The AUC of mAb [8,711 (mg/dL)*d, 95% CI: 6,511/10,911] and placebo [7,802 (mg/dL)*d, 95% CI: 6,289/9,316] did not differ ($P = 0.531$). Notably, the estimated effect of the treatment groups, concerning

baseline values, demonstrated a positive effect for mAb (estimate = 9.847 mg/dL, 95% CI: 5.494/14.201, $P < 0.001$). Calculated delta values differed at visits D1–D50 ($P = 0.001$) and D1–D78 ($P = 0.002$) between the study groups.

In addition, no significant differences in TG levels were observed within or between the treatment groups.

In summary, an increase in total, LDL, and HDL cholesterol was observed during mAb therapy in contrast to placebo. The observed effect was transient and the values returned to baseline levels after therapy completion. The course of the blood lipids is offered in Figure 2.

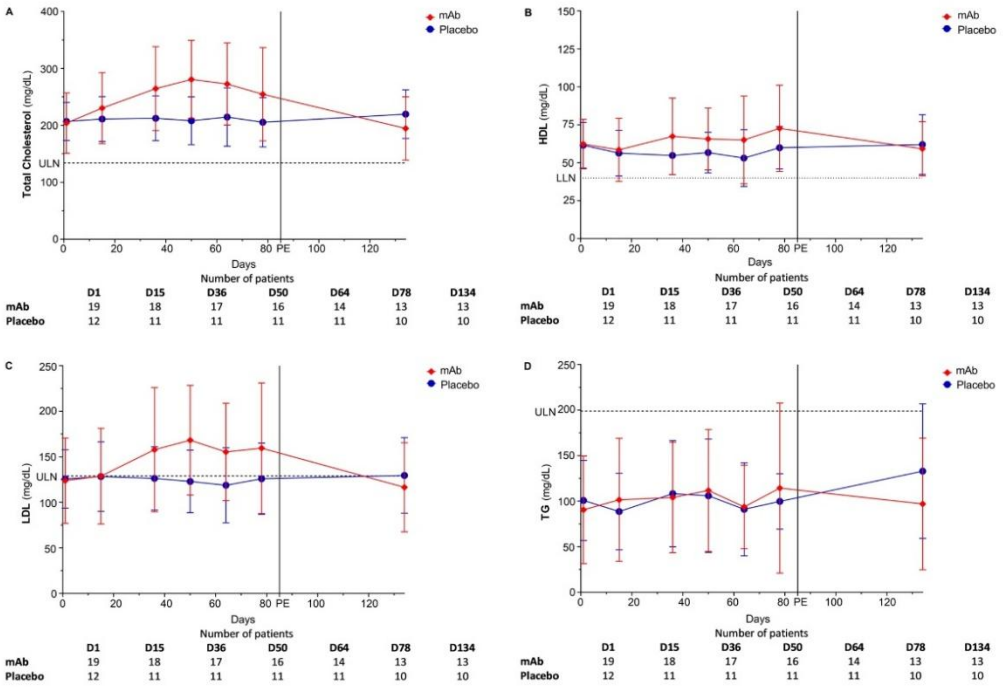


Figure 2. Course of blood lipids. (A) Total cholesterol: LLN = 0 mg/dL, ULN = 119 mg/dL; (B) HDL: LLN < 40 mg/dL; (C) LDL: LLN = 0 mg/dL, ULN = 129 mg/dL; (D) TG: LLN = 0 mg/dL, ULN = 199 mg/dL. D: day; HDL: high-density lipoprotein; LDL: low-density lipoprotein; LLN: lower limit of normal (dotted line); mAb: monoclonal antibody; PE: primary endpoint; TG: triglyceride; ULN: upper limit of normal (dashed line)

Liver function

The analyzed liver values encompass: alanine aminotransferase (ALAT), alkaline phosphatase (AP), aspartate aminotransferase (ASAT), and gamma-glutamyltransferase (γGT).

A mAb-induced AP increase was noted already after the first injection. Compared to D1, AP was higher at D50 ($P = 0.018$, peak level). Serum AP spontaneously and gradually normalized after treatment completion (AP_{D1} vs. AP_{D134}, $P > 0.999$). The estimation of treatment duration showed a positive effect (estimate = 0.167 U/L, 95% CI: 0.040/0.295, $P = 0.011$). The delta values D1–D50 and D1–D78 were not different ($P > 0.999$). In contrast, the delta values between D78–D134 and D1–D50, as well as D1–D78, exhibited relevant differences ($P = 0.030$ and $P = 0.018$). On placebo, no effect was observed between individual visits, among the delta values, or for treatment duration (estimate = –0.012 U/L, 95% CI: 0.105/0.080, $P = 0.788$). The AUC for mAb [12,427 (U/L)*d, 95% CI: 10,087/14,761] and placebo [10,207 (U/L)*d, 95% CI: 8,606/11,808] did not differ ($P = 0.153$). Compared to the placebo, the mAb estimated effect showed a positive effect, relative to baseline values (estimate = 13.790 U/L, 95% CI: 6.548/21.033,

$P < 0.001$). The two groups differed at visit D50 ($P = 0.015$) but not at visits D78 ($P = 0.237$) or D134 ($P = 0.552$). Delta values further differed at D1–D50 ($P < 0.001$) and D1–D78 ($P = 0.014$).

mAb increased γGT, peaking at D64 (γGT_{D1} vs. γGT_{D64}, $P > 0.999$), with values spontaneously normalizing (γGT_{D1} vs. γGT_{D134}, $P > 0.999$). The estimated effect for treatment duration, dependent on the baseline value, resulted in a positive effect (estimate = 0.008 U/L, 95% CI: −0.075/0.091, $P = 0.850$). The delta values between D1–D50 and D1–D78 did not differ ($P > 0.999$). However, this was the case between D1–D134 and D1–D50, as well as D1–D78 ($P = 0.014$ and $P = 0.201$, respectively). On placebo, no differences were noted. The estimated effect for treatment duration showed a negative effect (estimate = −0.022 U/L, 95% CI: −0.046/0.002, $P = 0.075$). The AUC for the anti-FcRn mAb [2,958 (U/L)*d, 95% CI: 1,577/4,338] was lower compared to placebo [1,835 (U/L)*d, 95% CI: 1,495/2,175], but the two areas did not differ ($P = 0.176$). The estimated effect of the treatment arm, considering baseline values, indicated a positive effect for the mAb (estimate = 5.456 U/L, 95% CI: −3.616/14.527, $P = 0.228$). While the groups did not show significant differences at each visit, they differed in the delta values of D1–D50 ($P = 0.017$) and D1–D78 ($P = 0.046$).

Finally, no differences were observed in the course of the respective groups or between the groups for ASAT and ALAT.

Taken together, no significant differences were observed between or within the groups for the parameters ASAT, ALAT, and γGT. However, there was a mAb-induced transient and significant increase in AP compared to placebo. The course of each parameter is illustrated in Figure 3.

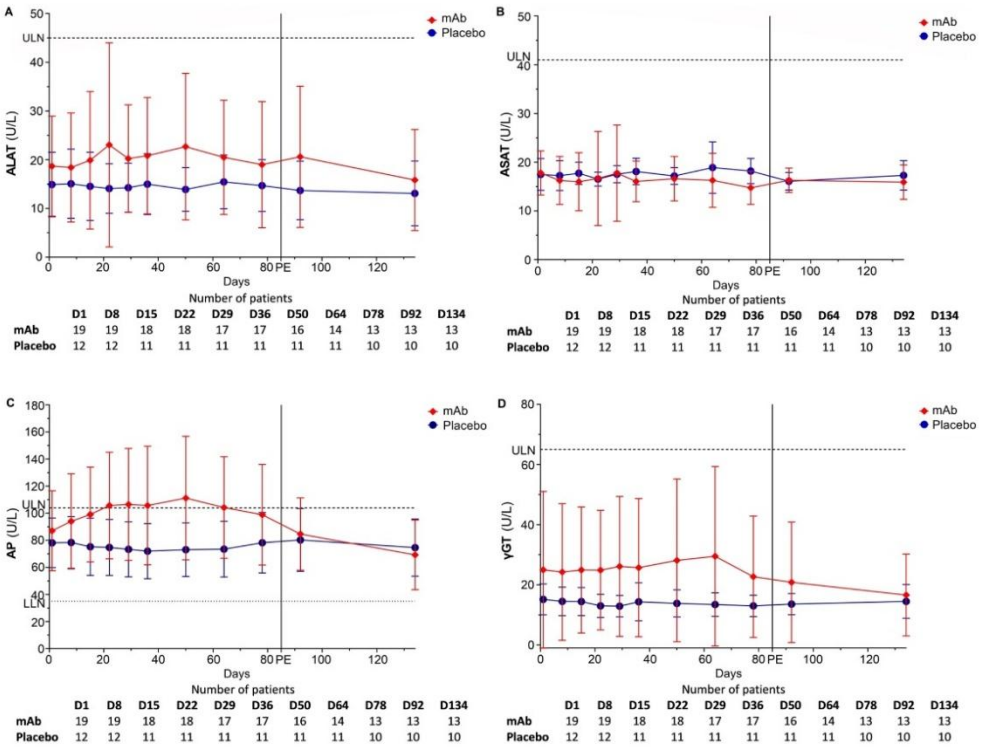


Figure 3. Course of liver enzymes. (A) ALAT: LLN = 0 U/L, ULN = 45 U/L; (B) ASAT: LLN = 0 U/L, ULN = 41 U/L; (C) AP: LLN = 35 U/L, ULN = 104 U/L; (D) γGT: LLN = 0 U/L, ULN = 65 U/L. γGT: gamma-glutamyltransferase; ALAT: alanine aminotransferase; AP: alkaline phosphatase; ASAT: aspartate aminotransferase; D: day; LLN: lower limit of normal (dotted line); mAb: monoclonal antibody; PE: primary endpoint; ULN: upper limit of normal (dashed line)

Blood cell titers & complement factors

No differences were observed between both groups or within each group for blood cell titers (lymphocytes, monocytes, platelets, and white blood cells) or complement factors (CH50 and C3c).

Correlations

The mAb-induced decrease of HSA negatively correlated with increasing levels of total (r = –0.893, P = 0.012), LDL (r = –0.750), and HDL-cholesterol (r = –0.656). Positive correlations between total cholesterol and both HDL (r = 0.571, P = 0.200) and LDL (r = 0.857, P = 0.024) were observed. Serum LDL and HDL cholesterol also correlated (r = 0.786, P = 0.048). In the placebo group, no significant effects were noted: HSA vs. total cholesterol (r = –0.143, P = 0.783), HSA vs. both HDL (r = 0.619, P = 0.138) and LDL (r = 0.143, P = 0.783). Mild negative (r = –0.214, P = 0.662) and positive correlations (r = 0.286, P = 0.556) between total cholesterol and HDL/LDL were observed (Figures 4 and 5). In the placebo group, a moderate positive correlation between LDL and HDL values was registered (r = 0.429, P = 0.354). In both groups, positive correlations between AP and γGT were noted in the mAb (r = 0.755, P = 0.001), and placebo (r = 0.192) groups (Table 4).

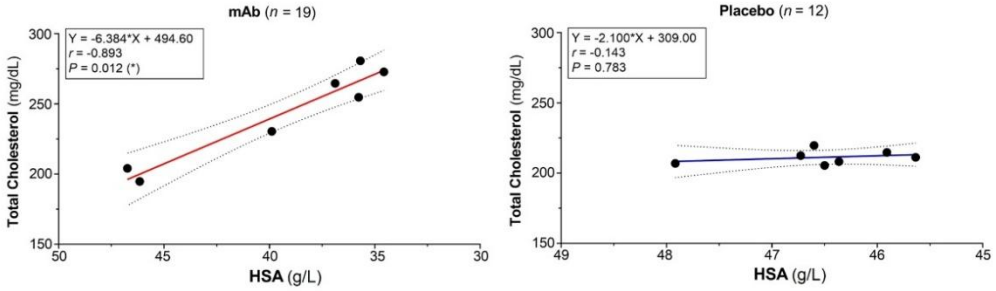


Figure 4. Negative correlation albumin-cholesterol. 95% Confidence interval is shown as dotted lines. * Significant difference. *n*: number of patients/events; *r*: Spearman's correlation coefficient (minor: 0.1 < *r* < 0.3; moderate: 0.3 < *r* < 0.5; high: *r* > 0.5). HSA: human serum albumin; mAb: monoclonal antibody

Discussion

AID characterized by the presence of autoantibodies usually correlates clinically with the serum titers of these AAb [31–33]. In animal experiments, AAb-induced AID can be triggered by their administration. The majority of AAbs belong to the IgG subgroup. Reducing IgG levels in these experiments resulted in a milder course of the diseases [19–21]. Under physiological conditions, the FcRn serves as an essential enzyme for maintaining IgG titers and a functional immune defense. FcRn selectively extends the half-life of IgG and HSA through a recycling mechanism. Experiments with FcRn-deficient mice have shown that mice lacking FcRn do not develop AAb-dependent AID or, in cases of very high serum titers, exhibit a comparatively milder form [19–21].

TA is characterized by thyroid AAbs, e.g., anti-thyroperoxidase and anti-thyroglobulin antibodies. These AAb, having an IgG phenotype, may lead to thyroid dysfunction and remodeling of the thyroid tissue [34–37]. The fact that selective reduction of IgG AAb can improve AID qualifies the FcRn as a potential target for the treatment of TA. The here-tested fully human mAb exhibits high selectivity for the FcRn and, through Fc modifications, has low cell-mediated cytotoxicity and complement-dependent cytotoxicity. Our exploratory study aimed to assess the safety and tolerability of this anti-FcRn mAb in patients with TA within a randomized, placebo-controlled phase 2 trial [29]. Besides our tested mAb, other substances targeting FcRn are currently undergoing clinical trials [22–28]. To account for a possible group effect of these substances targeting FcRn, we also considered parameters influenced by these substances in other clinical studies (HSA, blood lipid levels, and complement factors).

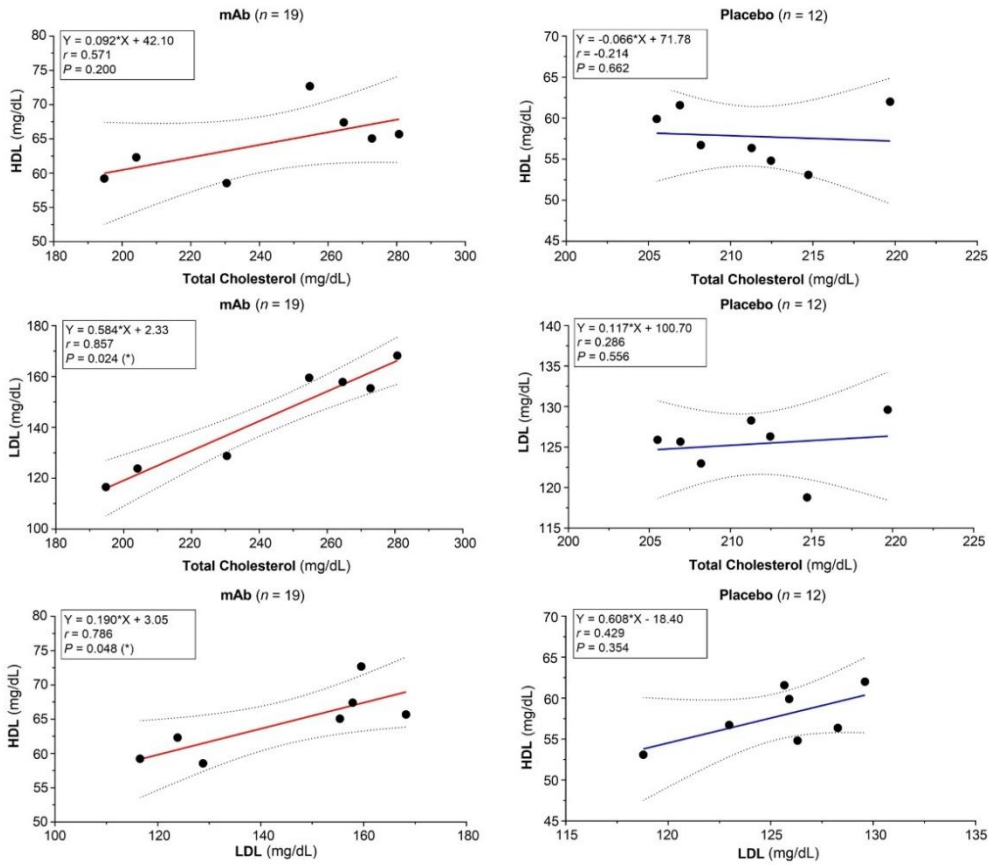


Figure 5. Correlation of blood lipids. 95% Confidence interval is shown as dotted lines. * Significant difference. *n*: number of patients/events; *r*: Spearman's correlation coefficient (minor: 0.1 < *r* < 0.3; moderate: 0.3 < *r* < 0.5; high: *r* > 0.5). HDL: high-density lipoprotein; LDL: low-density lipoprotein; mAb: monoclonal antibody

The mAb-induced decrease in HSA concentration correlating with an elevation of total and LDL cholesterol is clinically known. Patients with analbuminemia (idiopathic hypoalbuminemia) due to a genetic defect are unable to produce HSA or only minimal amounts [38–41]. Clinically, these patients exhibit elevated total and LDL cholesterol with minimally elevated HDL and TG. Symptomatically, patients experience peripheral edema and often fatigue. Similarly, in the nephrotic syndrome, significant loss of blood proteins like HSA occurs due to impaired blood filtration [42–46], resulting in increased total and LDL cholesterol levels, while HDL remains unchanged.

The significant loss of albumin likely leads to reduced breakdown and increased synthesis of lipids [41, 46, 47]. In vitro studies suggest a pseudoesterase activity for HSA, leading to the breakdown of acetyl coenzyme A (acetyl-CoA) [48]. With reduced HSA, less acetyl-CoA is metabolized, and more cholesterol is produced by the 3-hydroxy-3-methyl-glutaryl-CoA reductase (HMG-CoA reductase) [47, 48]. Due to albumin's partly hydrophobic structure, it can bind to lipophilic substances such as fatty acids and transport these peripherally. The loss of HSA leads to the redistribution of fatty acids onto lipoproteins, resulting in increased serum LDL and very low-density lipoprotein (VLDL) concentrations [41, 47, 49]. These mechanisms were confirmed in a mouse model with albumin-deficient mice [50]. However, a few studies in animal experiments also observed an increase in ASAT. The fact that FcRn can bind and recycle HSA, similar to IgG, suggests that the mAb-caused inhibition leads to an HSA deficit. Ligands at FcRn have different binding epitopes that do not hinder each other [51–53]. One possible cause for HSA loss by our

Table 4. Spearman's correlation matrix

Parameter 1	Parameter 2	Spearman correlation (*r*)	Interpretation (Cohn's criteria)	*P*-value
Monoclonal antibody				
HSA	Cholesterol total	–0.893	Negative correlation High correlation	0.012 (*)
HSA	HDL	–0.656	Negative correlation High correlation	0.110
HSA	LDL	–0.750	Negative correlation High correlation	0.066
Cholesterol total	HDL	0.571	Positive correlation High correlation	0.200
Cholesterol total	LDL	0.857	Positive correlation High correlation	0.024 (*)
LDL	HDL	0.786	Positive correlation High correlation	0.048 (*)
γGT	AP	0.755	Positive correlation High correlation	0.001 (**)
Placebo				
HSA	Cholesterol total	–0.143	Negative correlation Weak correlation	0.783
HSA	HDL	0.619	Positive correlation High correlation	0.138
HSA	LDL	0.143	Positive correlation Weak correlation	0.783
Cholesterol total	HDL	–0.214	Negative correlation Weak correlation	0.662
Cholesterol total	LDL	0.286	Positive correlation Weak correlation	0.556
LDL	HDL	0.429	Positive correlation Moderate correlation	0.354
γGT	AP	0.192	Positive correlation Weak correlation	0.570

* Significant difference; ** highly significant difference. *n*: number of patients/events. γGT: gamma-glutamyltransferase; AP: alkaline phosphatase; HDL: high-density lipoprotein; HSA: human serum albumin; LDL: low-density lipoprotein

tested mAb could be that after completing the recycling cycle, FcRn remains longer in a blocked state on the cell surface. The mAb-induced transient increase of γGT and AP suggests a potential mAb effect on the biliary system. However, based on the available data, it is challenging to determine whether the bile disorder was caused by an increase in cholesterol levels.

The two SAEs in the mAb group were deemed as "not drug-related". First, DON is regarded as an ophthalmic deterioration of TA. Second, there is no evidence (preclinical experiments or clinical studies) that FcRn inhibition may cause CNS inflammation. The expression of FcRn was demonstrated in the blood-brain barrier, but not directly in the CNS [54, 55]. Animal models demonstrated that FcRn plays an important role in the efflux or IgGs from immune-privileged organs like the CNS [56]. However, there are no convincing facts that the post-viral encephalitis was drug-induced. The consulting neurologists and the neurological tests clearly highlighted the most probable viral etiology.

The tested mAb was accompanied by atypical AE, e.g., headaches, nausea, and diarrhea. In other clinical studies using anti-FcRn compounds, AEs were mostly classified as mild to moderate [22–28, 57]. In contrast to previous reports, the difference in safety assessment focuses on blood lipid levels. None of the other studies described whether there was a change in cholesterol or LDL/HDL.

Several limitations of the present exploratory work ought to be discussed: (a) the non-prospective nature of the study, (b) the three treatment arms were combined in comparison with placebo, (c) the relatively small total number of treated and evaluated patients, due to the early termination of the trial. Further, it should also be emphasized that only patients at one center of the multicenter trial are evaluated in our work; with a higher number of included patients, statistical power usually increases while potential bias will decrease, (d) statistical analyses were neither prospectively defined nor controlled for multiplicity, and (e) different doses of the mAb could have varied with dose-dependent effects on serological parameters, e.g., HSA and blood lipid levels. Due to the low number of patients per group, a dose-dependent effect could not be evaluated.

Overall, the administered mAb can be considered safe and well-tolerated. Supportive, temporary therapy with cholesterol-lowering agents (such as statins) during the anti-FcRn mAb treatment might be beneficial. Further studies assessing the safety of the here-tested mAb for treating antibody-mediated AID are warranted.

Abbreviations

95% CI: 95% confidence interval

AAb: autoantibody

AEs: adverse events

AID: autoimmune diseases

ALAT: alanine aminotransferase

AP: alkaline phosphatase

ASAT: aspartate aminotransferase

AUC: area under the curve

CNS: central nervous system

CoA: coenzyme A

D1: day 1

DON: dysthyroid optic neuropathy

FcRn: neonatal crystallizable fragment receptor

GCP: Good Clinical Practice

HDL: high-density lipoprotein

HSA: human serum albumin

ICH: International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC: independent Ethics Committee

IgG: immunoglobulin G

LDL: low-density lipoprotein

mAb: monoclonal antibody

MedDRA: Medical Dictionary for Regulatory Activities

MP: methylprednisolone

SAE: serious adverse event

SEs: side effects

TA: thyroid autoimmunity

TGs: triglycerides

γGT: gamma-glutamyltransferase

Supplementary materials

The supplementary material for this article is available at: https://www.explorationpub.com/uploads/Article/file/1003145_sup_1.pdf.

Declarations

Author contributions

JW: Conceptualization, Data curation, Visualization, Writing—original draft, Writing—review & editing. IK: Validation, Writing—review & editing. GJK: Conceptualization, Investigation, Validation, Writing—original draft, Writing—review & editing, Supervision.

Conflicts of interest

GJK consults for Immunovant, Inc., New York City, NY, USA. The other authors declare that they have no conflicts of interest.

Ethical approval

The ASCEND GO 2 study was approved by the leading Ethics Committee (Rhineland Palatinate, 2019-14297-AMG).

Consent to participate

Informed consent to participate in the study was obtained from all participants.

Consent to publication

Not applicable.

Availability of data and materials

The raw data supporting the conclusions of this manuscript will be made available by the authors, without undue reservation, to any qualified researcher.

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2.2 Manuscripts submitted for publication and under revision

2.2.1 Secukinumab in Moderate-to-Severe Graves' Orbitopathy: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study

Submitted for publication in: The Journal of Clinical Endocrinology & Metabolism, 06.October.2025

Summary:
The manuscript presents data from the randomized, placebo-controlled, multicenter, double-blind phase 3 trial CAIN457ADE16 (ORBIT) and the open label extension (OLE) of the trial. In this phase 3 trial patients with moderate-severe, active EO were treated with the anti-IL-17 mAb Secukinumab. Patients were treated over a twelve-week period with Secukinumab or placebo. Non-responders at week 16 (primary) endpoint were offered to participate in the OLE phase.

Secukinumab showed neither clinically meaningful efficacy after the twelve-week double-blind treatment period nor during the subsequent open label treatment period. Over the entire study duration patients treated with Secukinumab showed no improvement in either EO related signs and symptoms, thyroid metabolic state, or quality of life. The study was terminated prematurely by the sponsor due to lack of efficacy.

The Secukinumab safety profile in ORBIT study was consistent with that reported in earlier trials in different autoimmune conditions. All AEs were mild-moderate and transient and no new safety signals were observed.

The ORBIT trial was the first clinical trial evaluating the efficacy of IL-17A inhibition in patients with moderate-severe, active EO.

Contributions:

- Drafting the study design
- Study coordination and organization
- Data reporting
- Drafting the manuscript
- Critical evaluation and revision

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SECUKINUMAB IN MODERATE-TO-SEVERE GRAVES' ORBITOPATHY: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY

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EudraCT no.: 2020-001611-24

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ABSTRACT

Context: Interleukin (IL) 17, a key pro-inflammatory cytokine, drives inflammation and fibrosis in Graves' orbitopathy (GO), and elevated IL-17 and Th17 cells correlate with disease activity and severity.

Objective: The ORBIT study aimed to evaluate the efficacy and safety of secukinumab, an IL-17A inhibitor, in subjects with active, moderate-to-severe GO.

Design: Randomized, double-blind, placebo-controlled, parallel-group, multicenter trial

Patients and methods: Adults with active, moderate-to-severe, non-sight–threatening GO randomly (1:1) received secukinumab 300 mg or placebo subcutaneously over a 16-week double-blind treatment period, followed by an additional 16-week open-label treatment phase for proptosis non-responders. Safety parameters, thyroid-related hormones, and autoantibodies were also assessed.

Primary endpoint: Overall response of reduced clinical activity score (CAS) of ≥2 points and reduction of ≥2 mm in proptosis from baseline without worsening in the fellow eye at Week 16.

Results: 28 adults with a CAS ≥4 were enrolled (secukinumab, n=14; placebo, n=14). None in either the secukinumab or placebo group achieved an overall response at Weeks 16 and 32, respectively, when all patients received open-label secukinumab. No clinically meaningful changes were observed in ophthalmic symptoms and signs, proptosis, lid aperture, eye muscle motility, CAS, and health-related quality of life either at Week 16 or Week 32. No meaningful impact on serum levels of thyroid-related hormones and antibodies was observed. Secukinumab was well tolerated, with mostly mild adverse events. No new safety signals were registered.

Conclusion: Secukinumab did not show clinical efficacy versus placebo when treating patients with active, moderate-to-severe GO.

Key words: Interleukin-17A, Secukinumab, Graves' orbitopathy, ORBIT trial, active, moderate-to-severe GO, immunosuppressive treatment

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INTRODUCTION

Graves' orbitopathy (GO), also known as thyroid eye disease (TED), is a rare organ-specific autoimmune disorder characterized by inflammation and tissue remodeling within the orbits (1-3). The disease causes significant functional impairment (e.g., lid retraction leading to lagophthalmos with corneal affection and/or diplopia) along with disfiguring proptosis, and can be sight threatening in severe cases (2, 4). GO significantly impacts patients' quality of life and work productivity (5-7). The management of moderate-to-severe GO remains a major clinical and therapeutic challenge (8). Given the very limited number of available and approved treatment options, there is a significant unmet medical need for more effective and targeted therapies to manage severe GO, prevent complications, and improve long-term patient outcomes (9). Clinicians can observe robust effects with non-specific treatment options in approximately two-thirds of the patients, depending on the manifestations and applied treatment type. The treatment benefit may be of short duration and limited by occurring adverse events (1). Side effects vary depending on the type of treatments and therapeutic targets. Most of the immunosuppressive agents cause loss of function of the immune system depending on the target (e.g., neutropenia and thrombocytopenia with tocilizumab, loss of B cell function with rituximab), whereas insulin-like growth factor 1 receptor blockade may induce hearing impairment, dry skin, hair loss, and bowel problems (10). Consequently, the need for novel therapies is driven by the significant impact of the disease on patients' quality of life, the limitations of currently available treatments, and emerging therapies that can target the pathogenic processes involved more precisely (11, 12).

Dysregulated T-cell (TC) immunity and autoreactive TCs are involved in orbital inflammatory processes (13). Additionally, innate autoimmunity, M1-like macrophages and dendritic cells (DC), sustain the autoimmune response and the perpetuating tissue damage through the interleukin (IL)-6 and IL-17 signaling pathways (14). IL-17A, a pro-inflammatory cytokine, promotes fibrosis, enhances pro-inflammatory cytokine production, and interacts with orbital fibroblasts (OF) to support the differentiation of IL-17 producing TC (Th17 TC) (4, 15-17). Moreover, IL-17 levels and Th17 TC correlated with the clinical activity and severity of GO, with higher IL-17 levels associated with more active and severe disease (18-22).

Secukinumab, a recombinant, high-affinity, fully human monoclonal antibody that selectively targets and blocks IL-17A, is a potential, targeted therapeutic option for GO. Inhibition of IL-17A could reduce orbital inflammation and prevent progression of tissue damage. Herein, we report the findings of the "ORBIT" study, that evaluated the efficacy and safety of subcutaneous (s.c.) secukinumab 300 mg in adults with clinically active, moderate-to-severe GO. The primary objective of this study was to demonstrate that secukinumab is superior to placebo in reducing the signs and symptoms of moderately-severe GO after 16 weeks of treatment.

MATERIALS AND METHODS

Study design

This was a randomized, placebo-controlled, double-blind, parallel-group, interventional, multicenter study in adult patients with clinically active, moderate-to-severe GO (EudraCT no. 2020-001611-24). The study consisted of a screening period (6 weeks), a double-blind treatment period (16 weeks), and an open-label re-treatment/follow-up period (**Supplementary Figure 1**).

Eligible patients were randomized in a 1:1 ratio and stratified according to current smoking status to receive secukinumab 300 mg s.c. or placebo (at baseline and weeks 1, 2, 3, 4, 8, and 12) during the 16 weeks double-blind treatment period. At Week 16, patients with a proptosis response (*proptosis responders*) were followed up for up to Week 68, and during this time those who had a relapse were offered a course of open-label secukinumab at the time of relapse. At Week 16, patients who did not achieve a proptosis response (*proptosis non-responders)* could enter an open label treatment phase and receive an additional course of secukinumab 300 mg s.c. (with maintenance of blinding to the initial

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randomized treatment) for a duration of 16 weeks, i.e., up to Week 32. From Week 32, patients were followed for further 24 weeks to assess relapse and safety (up to Week 56). Proptosis response at Week 16 was defined as a reduction in proptosis of ≥2 mm from baseline in the more severely affected (study) eye without deterioration (≥2 mm increase) of proptosis in the fellow eye. Relapses were defined as an increase in proptosis of ≥2 mm compared to Week 16 in the study eye or deterioration of proptosis (≥2 mm increase) in the fellow eye at any time during the 52-week follow-up period.

Study population

The study included males and females aged ≥18 years with clinically active, moderate-to-severe, non-sight–threatening GO. Patients were required to have a Clinical Activity Score (CAS) ≥4. Moderate-to-severe GO was defined according to the European Group on GO (EUGOGO) guidelines (1) and stratification, with at least two of the following signs: lid retraction ≥2 mm, moderate or severe soft tissue involvement, proptosis of ≥3 mm above normal, or diplopia (inconstant or constant). The onset of GO symptoms and signs must have been within 12 months prior to the baseline assessment. Peripheral biochemical euthyroidism or mild hypo-/hyperthyroidism (free T3 [fT3] and free T4 [fT4]) serum levels being less than 30% above or below normal limits) at the time of screening and orbital magnetic resonance imaging (MRI) assessment to confirm diagnosis of GO were required.

The study excluded patients who exhibited an improvement in CAS ≥2 points or in proptosis ≥2 mm in the study eye between screening and baseline. Patients showing signs of sight-threatening GO were also excluded. Additionally, patients requiring immediate or urgent surgical intervention or glucocorticoid treatment and those who had previously undergone orbital radiotherapy, orbital surgery for GO, or used biological or immunomodulatory agents for the treatment of GO were excluded.

Study endpoints and assessments

The primary endpoint was the proportion of patients achieving overall response, defined as a reduction of ≥2 points in CAS and ≥2 mm in proptosis from baseline ("composite index") in the study eye, with no deterioration in CAS or proptosis (increase of ≥2 points or 2 mm, respectively) in the fellow eye after the 16 weeks treatment. The secondary endpoints of the study were CAS responder rate, proptosis responder rate, reduction in diplopia (baseline diplopia >0 and a reduction of ≥1 grade with no deterioration [≥1 grade worsening] in the fellow eye at Week 16), mean change from baseline in CAS in the study eye, mean change from baseline in proptosis in the study eye, improvement in the EUGOGO disease severity, improvement in GO quality of life (GO-QoL), and safety of secukinumab compared to placebo based on the frequency of adverse events (AE), treatment-emergent AE (TEAE), AE resulting in treatment discontinuation, and serious AE (SAE).

Serum samples were collected for the assessment of thyroid related hormones and autoantibodies throughout the duration of the study.

Statistical analysis

The study planned to enroll 70 patients to achieve 90% power for demonstrating the superiority of secukinumab at a 0.05 significance level, using a two-group continuity-corrected Chi-square test. The study was terminated early on 16-Feb-2023 after a blinded review, and statistical analysis of data from 23 patients who completed the 16-weeks treatment indicated a very low likelihood of achieving the primary efficacy endpoint. Consequently, the analysis plan was revised to omit superiority testing and descriptive analyses were performed. Demographic and other baseline data including disease characteristics and efficacy endpoints were performed on the full analysis set, comprising all patients who received study treatment (secukinumab or placebo) as per the original randomization. Week 16 and Week 32 efficacy data were included in the analyses, regardless of premature discontinuation of study treatment. The safety

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analysis set included all patients who received at least one dose of study treatment during the treatment period. Missing values were not replaced, and no sensitivity or subgroup analyses were performed.

Ethics statement

The study protocol was reviewed by the independent ethics committee or institutional review board for each center, and the study was conducted in accordance with the International Council for Harmonization E6 Guideline for Good Clinical Practice and Declaration of Helsinki. All patients provided written informed consent before inclusion in the study. The ethics committee approval was received from the lead investigator's study site (JGU Medical Center, Mainz, Germany).

RESULTS

Patient disposition

Overall, 33 patients with clinically active, moderately-severe GO were screened, and 28 patients were randomized in a 1:1 ratio to the two treatment groups. Of the randomized patients, 24 (85.7%) completed the double-blind treatment period and 17 (60.7%) completed the open-label phase. The study was terminated early, with nine patients (32%) completing the Week 56 follow-up visit (**Supplementary Figure 2**). Patient disposition by treatment group is summarized in the supplementary results.

Demographics and baseline characteristics

The two treatment groups were generally balanced with respect to baseline characteristics (**Table 1**). The placebo group had more females, lower mean body weight, and shorter median time since diagnosis of GO compared to the secukinumab group. There were no notable differences in disease severity parameters between the two groups at baseline. Thyroid function and related autoantibodies were generally similar. Two patients in each group had thyroidectomy prior to study enrollment.

Table 1 Demographics and baseline characteristics

	SECUKINUMAB (N= 14)	**PLACEBO (N= 14)**
Age (years, mean ± SD)	53.6 ± 11.85	57.7 ± 10.64
Female, n (%)	9 (64.3)	12 (85.7)
Caucasian, n (%)	14 (100)	14 (100)
Weight (Kg, mean ± SD)	88.3 ± 21.56	77.5 ± 19.31
Height (cm, mean ± SD)	169.3 ± 11.25	169.2 ± 10.77
Smoking history, n (%)		
Current	3 (21.4)	4 (28.6)
Former	8 (57.1)	6 (42.9)
Never	3 (21.4)	4 (28.6)
Time since the first diagnosis of GO (years), median (min-max)	0.7 (0.2-0.9)	0.4 (0.1-0.7)
Underlying thyroid condition, n (%)		
Graves' disease	14 (100.0)	12 (85.7)
Hashimoto's thyroiditis	0	2 (14.2)
Thyroid medications, n (%)[a,b]	10 (71.4)	7 (50.0)
Levothyroxine[c]	2 (14.3)	3 (21.4)
Anti-thyroid thionamide drugs (carbimazole, thiamazole, propylthiouracil)[c]	9 (64.3)	5 (35.7)
No thyroid medication, n (%)	4 (28.6)	7 (50.0)

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CAS (mean ± SD)	5.4 ± 1.01	5.4 ± 1.01
CAS symptoms and signs, n (%)		
Spontaneous retrobulbar pain present	12 (85.7)	14 (100.0)
Pain on attempted upward/downward gaze present	12 (85.7)	13 (92.9)
Swelling of the eyelids present		
Mild	8 (57.1)	4 (28.6)
Moderate	5 (35.7)	6 (42.9)
Severe	1 (7.1)	3 (21.4)
Swelling of the conjunctiva present		
Mild	5 (35.7)	6 (42.9)
Moderate	3 (21.4)	3 (21.4)
Severe	0	0
Swelling of the caruncle or plica present	10 (71.4)	8 (57.1)
Redness of the eyelids present	5 (35.7)	4 (28.6)
Conjunctival redness present		
Mild	7 (50.0)	7 (50.0)
Moderate	6 (42.9)	5 (35.7)
Severe	1 (7.1)	2 (14.3)
Proptosis (mm, mean ± SD)	21.9 ± 4.12	21.1 ± 3.06
Diplopia grade, n (%)		
No diplopia	4 (28.6)	6 (42.9)
Intermittent	1 (7.1)	0
Inconstant	4 (28.6)	4 (28.6)
Constant	5 (35.7)	4 (28.6)
GO-QoL (mean ± SD)		
Visual functioning	64.1 ± 23.04	66.6 ± 24.38
Appearance	65.6 ± 22.43	60.3 ± 20.60
Thyroid-related parameters		
Serum fT3 (pmol/L)	4.7 ± 1.29	4.9 ± 1.23
Median (min-max)	4.4 (3.1-8.1)	4.5 (3.5-7.7)
Serum fT4 (pmol/L)	14.9 ± 5.36	15.6 ± 5.83
Median (min-max)	13.2 (8.9-25.6)	15.1 (3.5-25.1)
Serum TSH (mU/L)	2.1 ± 2.10	0.9 ± 2.05
Median (min-max)	1.2 (0.0-6.1)	0.4 (0.0-7.9)
Serum TBII (IU/L)	14.2 ± 11.20	23.5 ± 30.51
Median (min-max)	8.8 (1.4-33.3)	9.0 (1.4-91.9)
Serum TSAb (% SRR)	551.1± 140.57	519.1 ± 132.41
Median (min-max)	502.0 (381.0-778.0)	553.5 (172.0-706.0)
Anti-TPO antibodies (IU/mL)	59.6 ± 90.24	57.8 ± 73.72
Median (min-max)	20.4 (9.3-323.2)	18.6 (6.4-258.8)
Anti-TG antibodies (IU/mL)	150.4 ± 240.46	589.4 ±1828.73
Median (min-max)	17.3 (10.1-768.4)	55.0 (11.9-6928.0)

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Data are presented as mean ± SD unless otherwise specified. Analysis based on full analysis set consisting of all patients to whom study treatment (secukinumab or placebo) had been assigned. Following the intent-to-treat principle, patients were analyzed according to the treatment they had been assigned to.

[a]No patient received prior radioactive iodine treatment and 2 patients in each group had thyroidectomy prior to study enrollment. [b]Number of patients with at least one thyroid medication. [c]A patient was counted once in each category for which he/she received a medication. Therefore, a patient can be counted under both thyroid medications categories. One patient each in the secukinumab and placebo groups received both levothyroxine and anti-thyroid medications.

CAS, Clinical Activity Score; EUGOGO, European Group on Graves' Orbitopathy; fT3, serum free triiodothyronine; fT4, serum free thyroxine; GO, Graves' orbitopathy; Min, minimum; Max, maximum; n, number of patients; QoL, quality of life; SD, standard deviation; SRR, Specimen-to-Reference ratio; TBII, TSH-R binding inhibiting immunoglobulins; TSAb, TSH-R stimulating antibodies; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyrotropin; TSH-R, TSH receptor.

Efficacy

The primary endpoint was analyzed at Week 16 and Week 32. Of the 28 patients, five patients (18%) did not have a Week 16 assessment: one patient in the secukinumab group was lost to follow-up, three patients (one in the secukinumab group and two in the placebo group) had not reached Week 16 when the study was terminated early, and one patient in the placebo group did not have a Week 16 assessment and was therefore not included. Seven patients (three in the secukinumab group and four in the placebo-secukinumab group) did not have a Week 32 assessment.

No overall response was observed in either treatment group at both assessment time points (**Table 2**). There were no notable clinical responses in proptosis, diplopia or CAS, in either secukinumab- or placebo-treated patients from baseline to Week 16, as well as from Week 16 to 32 when all patients received open-label secukinumab treatment (**Table 2**). Thus, no meaningful changes were observed in proptosis, diplopia, and/or mean CAS during either the double-blind or open-label treatment period (**Figure 1**).

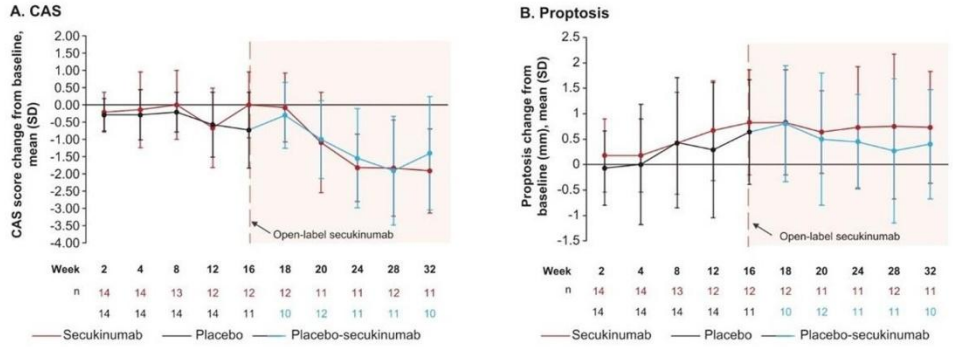

Figure 1 Change from baseline in clinical activity score (CAS) (A) and proptosis (B), during double-blind and open-label treatment periods

At each time point, only patients with values at baseline and at that time point are included.

CAS, Clinical Activity Score; n, number of patients at that svisit; SD, standard deviation.

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Table 2 Efficacy outcomes

	Week 16, End of the double-blind period		Week 32, End of the open-label retreatment period	
	Secukinumab (N= 14)	**Placebo (N= 14)**	**Secukinumab (N= 14)**	**Placebo-Secukinumab (N= 14)**
Primary endpoint				
Overall response[a], n (%)				
Yes	0	0	0	0
No	12 (100)	11 (100)	11 (100)	10 (100)
Missing[b]	2	3	3	4
Secondary endpoints				
Response in CAS reduction[a], n (%)				
Yes	0	3 (27.3)	8 (72.7)	5 (50.0)
No	12 (100)	8 (72.7)	3 (27.3)	5 (50.0)
Missing[b]	2	3	3	4
Response in proptosis reduction[c], n (%)				
Yes	0	0	0	0
No	12 (100)	11 (100)	11 (100)	10 (100)
Missing[b]	2	3	3	4
Response in diplopia reduction[d], n (%)				
Yes	1 (8.3)	1 (8.3)	2 (18.2)	3 (30.0)
No	11 (91.7)	11 (91.7)	9 (81.8)	7 (70.0)
Missing[b]	2	2	3	4

Analysis based on full analysis set consisting of all patients to whom study treatment (secukinumab or placebo) had been assigned. Following the intent-to-treat principle, patients were analyzed according to the treatment they have been assigned to.
[a]Overall response defined as a ≥2 points reduction in CAS and a ≥2 mm reduction in proptosis from baseline in the study eye, provided no corresponding deterioration in CAS or proptosis occurs in the fellow eye. [b]Response is missing if the patient discontinued the study before the assessment endpoint (Week 16 and Week 32, respectively). [c]Proptosis responder defined as a reduction of ≥2 mm from baseline in the study eye without deterioration (≥2 mm increase) of proptosis in the fellow eye. [d]Diplopia responder defined as baseline diplopia >0 and a reduction of ≥1 grade at Week 16.
CAS, Clinical Activity Score; n, number of patients.

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No improvement in EUGOGO disease severity between baseline and Week 16 was observed in both groups **(Supplementary Table 1)**. The GO-QoL subscale visual functioning and the psychosocially driven subscale appearance remained stable in the secukinumab group during both double-blind and open-label treatment periods. In comparison, slight increases in both scores were noted in placebo patients who received secukinumab in the open-label treatment from Week 16 to Week 32 (**Figure 2**).

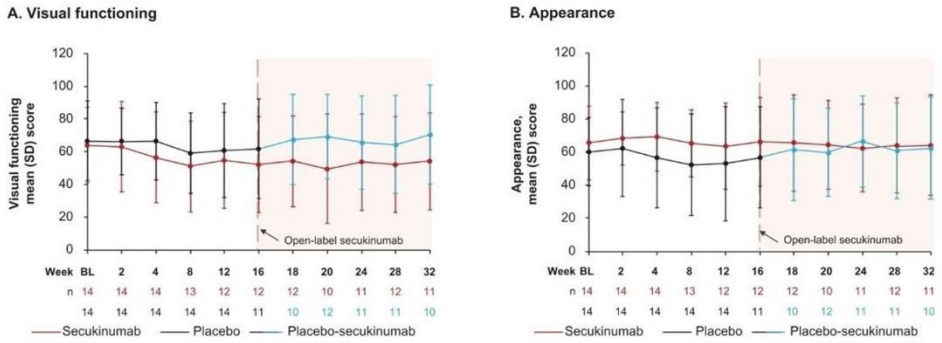

Figure 2 GO-quality of life (QoL) subscales visual functioning (A) and appearance (B), during double-blind and open-label treatment periods

At each time point, only patients with values at baseline and at that time point are included.
BL, baseline; GO-QoL, Graves' Orbitopathy Quality of Life; n, number of patients at that visit; SD, standard deviation.

Thyroid-related parameters

Overall, the mean serum levels of fT3, fT4, and thyrotropin (TSH) were comparable between the treatment groups and remained within the normal range over time in the double-blind and open-label phases (**Figure 3**). At baseline, serum levels of TSH-receptor (TSH-R) binding inhibiting (TBII) and TSH-R stimulating (TSAb) immunoglobulins exceeded normal cut-off values, and TSH-R blocking antibodies (TBAb) were negative throughout the study (data not shown). While, TBII levels remained unchanged during the entire study period, a trend towards decreased levels of TSAb from baseline was observed over the entire study period. At baseline, patients tested positive for thyroid peroxidase and thyroglobulin autoantibodies with antibody levels exceeding the normal cut-off limits and elevated antibody levels persisted throughout the entire study period (**Figure 4**).

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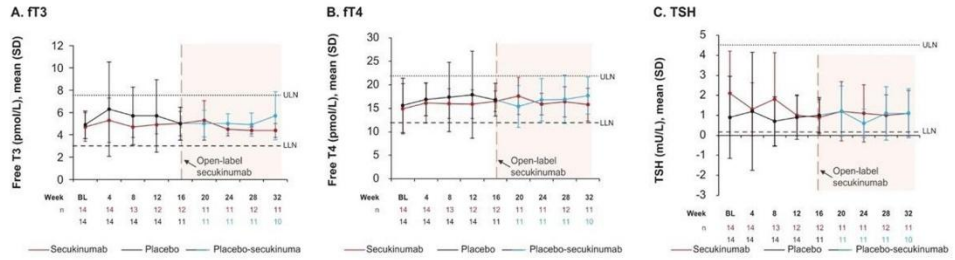

Figure 3 Thyroid-related parameters, serum free T3 (A), serum free T4 (B), and serum TSH (C), during double-blind and open-label treatment periods

At each time point, only patients with values at baseline and at that time point are included.
Dashed line: LLN, lower limit of normal: fT3= 3.08 pmol/L; fT4= 12.0 pmol/L; TSH= 0.27 mU/L
Dotted line: ULN, upper limit of normal: fT3= 6.78 pmol/L; fT4= 21.9 pmol/L; TSH= 4.20 mU/L
BL, baseline; fT3, free triiodothyronine; fT4, free thyroxine; TSH, thyrotropin; LLN, lower limit of normal; n, number of patients at that visit; SD, standard deviation; ULN, upper limit of normal.

Safety

The mean ± SD exposure to study drug in the secukinumab group was 235.0 ± 85.26 days (range: 29–282 days, median 279.5 days) versus 116.6 ± 9.52 days (range: 112–140 days, median 113 days) in the placebo group. During the double-blind treatment period, a higher proportion of patients in the secukinumab group had AE than that in the placebo group (64.3% vs 42.9%), and most AE in both treatment groups were mild (**Table 3**). None of the AE led to discontinuation of the study treatment. The most frequent TEAE by system organ class during the double-blind treatment period were infections and infestations in 4/14 patients (28.6%) in the secukinumab group and 5/14 patients (35.7%) in the placebo group. Only one SAE, worsening of GO, was reported in one patient (1/14; 7.1%) of the placebo group. During the double-blind treatment period, the most frequent TEAE reported in two or more patients, based on preferred term were COVID-19 infections and headache (**Supplementary Table 2**). One case of oral candidiasis and oral herpes was reported in the secukinumab group (1/14; 7.1% each). An overview of the TEAE that occurred during the entire study period by system organ class and preferred term is provided in **Supplementary Table 3**.

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Table 3 Safety - Double blind treatment (baseline to week 16)

n (%)	SECUKINUMAB (N= 14)	PLACEBO (N= 14)
Any AE	9 (64.3)	6 (42.9)
Mild	5 (35.71)	4 (28.57)
Moderate	4 (28.57)	1 (7.14)
Severe	0	1 (7.14)
Study treatment-related AEs	3 (21.4)	1 (7.1)
AE leading to study treatment discontinuation	0	0
Serious AEs	0	1 (7.1)
Worsening of GO*	0	1 (7.1)
TEAEs by SOC		
Infections and infestations	4 (28.6)	5 (35.7)
General disorders and administration site conditions	3 (21.4)	2 (14.3)
Eye disorders	2 (14.3)	2 (14.3)
Musculoskeletal and connective tissue disorders	2 (14.3)	2 (14.3)
Nervous system disorders	2 (14.3)	1 (7.1)
Investigations	1 (7.1)	1 (7.1)
Psychiatric disorders	2 (14.3)	0
Blood and lymphatic system disorders	1 (7.1)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (7.1)	0
Renal and urinary disorders	0	1 (7.1)
Skin and subcutaneous tissue disorders	1 (7.1)	0
Vascular disorders	1 (7.1)	0

The safety analysis set consisted of all patients who received at least one dose of study treatment during the treatment period. Patients were analyzed according to the study treatment received. A patient with multiple TEAE within a primary system organ class is counted only once in the total row. A patient with multiple occurrences of TEAE under one treatment is counted only once in this AE category for that treatment.

*The patient underwent orbital decompression surgery due to worsening of GO. The patient was treated with high doses of intravenous methylprednisolone pulses because of optic neuropathy and locally with ointments/drops containing povidone-iodine, dexamethasone, gentamicin, and hypromellose. Lack of efficacy to study treatment was reported as the contributing factor. Patient completed the double-blind phase of the study and then discontinued from the study.

AE, adverse event; GO, Graves' orbitopathy; n, number of patients; SOC, system organ class; TEAE, treatment-emergent adverse event.

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DISCUSSION

The ORBIT study was a well-conceived and executed, randomized, double-blind, placebo-controlled, multicenter trial designed to answer the question of whether inhibition of IL-17A is an appropriate treatment approach for patients with clinically active, moderate-to-severe, non sight-threatening GO. Over the 16-week double-blind treatment period, inhibition of IL-17A with secukinumab treatment did neither show efficacy versus placebo, nor did it show clinically meaningful efficacy in the subsequent 16-week open-label treatment period. Thus, prolonged drug exposure did not have a beneficial impact on disease severity nor on thyroid metabolic state, and the study was terminated prematurely due to the lack of efficacy.

Although there was no improvement in the primary endpoint, a decrease in CAS of at least 2 points was observed in 73% (8 of 11) and 50% (5 of 10) of the patients in secukinumab and placebo groups in the open-label phase, while 30% (3 of 10) of those randomized to placebo improved their diplopia after receiving open-label secukinumab treatment. A similar trend of improvement in GO-QoL visual functioning by ~10 points was seen in the placebo group after receiving open-label secukinumab treatment. However, these results are limited by the small sample size, due to early termination of the trial. Apparent effects—particularly regarding quality of life—may have been influenced by participants' awareness of receiving active treatment during the open-label extension. The data mirrors a potential trend only and should therefore be interpreted with caution.

The AE data in this study were consistent with the well-characterized safety profile of secukinumab reported in a broad range of clinical trials across different immune-mediated conditions, as well as real-world experience with secukinumab (23). All AE were mild to moderate and transient, and no new safety signals were observed in this study. The most common AE reported with secukinumab were headache, injection site reactions, nasopharyngitis, upper respiratory tract infections, and candida infections (23, 24). No increased incidence of infections was observed with secukinumab compared with placebo in the ORBIT trial. The most frequently reported infection in both groups was COVID-19 (four cases in the secukinumab and six cases in the placebo group). Considering the unusual conditions of the pandemic and the higher incidence observed in the placebo group, it seems unlikely that secukinumab increased the susceptibility to SARS-CoV-2.

The rationale for targeting IL-17A with the monoclonal antibody secukinumab in patients with moderate-to-severe GO was based on several pre-clinical and translational studies (19-21, 25). Key players in innate immunity, such as macrophages and DC, are essential for antigen presentation and the production of pro-inflammatory cytokines in GO. These cytokines include tumor necrosis factor, IL-1β, IL-6, IL-23, and B cell-activating factor (9). Orbital-infiltrating M1-like macrophages express IL-6 and are predominant in patients with active GO (14). DC are fundamental components of the autoimmunity cascade, playing crucial roles in regulating self-tolerance, inflammation, and the activation and differentiation of TC (26). Macrophages and DC also act as antigen-presenting cells contributing to the activation, proliferation and differentiation of T lymphocytes (14). Auto-reactive T lymphocytes targeting TSH-R-expressing OF contribute to the establishment and maintenance of autoimmunity, as well as tissue remodeling in GO (13, 15, 16, 26).

More specifically, Th17 TC, which express IL-17A, are significantly increased in the orbital tissue of patients with GO (15). Increased levels of IL-17A have been detected in serum and tears of patients with GO, positively correlating with disease activity (27). IL-17A has been shown to promote transforming growth factor beta (TGF-ß)-induced fibrosis in $CD90^+$ OF, contributing to the production of extracellular matrix proteins such as collagen and fibronectin, and inhibiting adipogenesis in $CD90^-$ OF. Both $CD90^+$ and $CD90^-$ OF contributed to Th17 TC differentiation through the production of prostaglandin E2. Th17 TC upregulated the expression of costimulatory molecules on OF, and thereby enhanced the immune reaction in the orbits (15, 19, 20). Hence, given the role of IL-17A and Th17 TC in GO, it seemed evident that blocking IL-17A could serve as an effective therapeutic target. However, the ORBIT study findings indicate that blocking a single cytokine does not sufficiently limit the complex, multifactorial inflammatory processes

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involved in GO. A better understanding of other key immune mediators in the disease pathophysiology is needed.

Secukinumab has been approved and is successfully and widely used in clinical practice for several immune-mediated conditions, including moderate-to-severe plaque psoriasis, psoriatic arthritis, axial spondyloarthritis, and hidradenitis suppurativa, with rapid and sustained clinical improvements (24, 28-30). Compared to these clearly Th17-mediated conditions, the results of this study could indicate that the Th17 axis is a less causal mechanism in GO, and other (e.g. more B cell-driven autoimmunity-related) processes are more dominant in GO.

In conclusion, inhibition of IL-17A with secukinumab did not show clinical efficacy versus placebo in the treatment of moderate-to-severe GO. AE were in line with the well-characterized safety profile of secukinumab, with no new signals observed. While previous translational studies indicated a role in GO, inhibition of IL-17A did not translate into clinical improvements in this study.

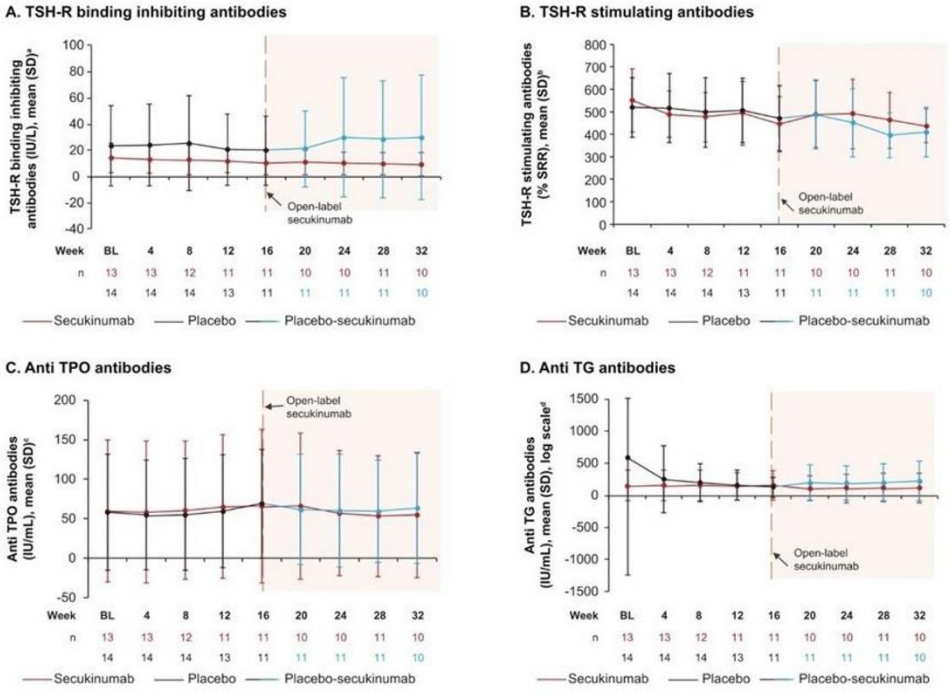

Figure 4 Changes in TSH-R binding inhibiting immunoglobulins (A), TSH-R stimulating antibodies (B), anti-thyroid peroxidase (TPO) antibodies (C), and anti-thyroglobulin (TG) antibodies (D), during double-blind and open-label treatment periods

[a]TSH-R binding inhibiting immunoglobulins, cutoff value= <1.75 IU/L. [b]TSH-R stimulating antibodies, cutoff value= <140 SRR%. [c]Anti-TPO antibodies, cutoff value= <34 IU/mL. [d]Anti-TG antibodies, cutoff value= <115 IU/mL.

BL, baseline; n, number of patients at that visit; SD, standard deviation; SRR, Specimen-to-Reference ratio; TG, thyroglobulin; TPO, thyroid peroxidase; TSH, thyrotropin; TSH-R, TSH receptor

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DATA AVAILABILITY

The authors declare that all data supporting the findings of this study are available within the manuscript and the Supplementary Material.

AUTHOR CONTRIBUTIONS

JW: Investigation, methodology, formal analysis, software, validation, visualization, writing—original draft, writing—review & editing.
KL: Investigation, methodology, formal analysis, validation, visualization, writing—review & editing.
AEO: Investigation, methodology, formal analysis, software, validation, visualization, writing—review & editing.
AB.: Investigation, methodology, visualization, writing—review & editing.
HMM: Investigation, methodology, visualization, writing—review & editing.
LG: Investigation, writing—review & editing.
HE: Investigation, writing—review & editing.
ML: Methodology, formal analysis, software, validation, writing—review & editing.
AE: Investigation, writing—review & editing
HL: Investigation, writing—review & editing
MS: Investigation, writing—review & editing
MH: Investigation, writing—review & editing
WAL: Investigation, writing—review & editing
TB: Investigation, writing—review & editing
SP: Investigation, writing—review & editing
CV: writing—review & editing
CCP: Data curation, methodology, writing—review & editing
BP: Data curation, resources, visualization, writing—review & editing.
AC: Data curation, methodology, project administration, resources, software, visualization, writing—review & editing.
SD: writing—review & editing
MR: Conceptualization, data curation, formal analysis, funding acquisition, methodology, resources, validation, visualization, writing—review & editing.
G.J.K.: Conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, resources, supervision, project administration, validation, visualization, writing—original draft, writing—review & editing.

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3 DISCUSSION

For the treatment of EO, only non-specific, non-causal treatment options are currently available. The rationale of the present thesis was to evaluate the safety and efficacy of two mAb as potential targeted treatment options. Batoclimab selectively inhibits the FcRn, which prolongs the half-life of both, IgG and aAb of the IgG-like TSH-R-Ab. TSH-R-Ab cause an overstimulation of the TSH-R, the primary auto-antigen in EO. Enhanced degradation of the IgG-like TSH-R-Ab results in an inhibition of the uncontrolled activation of thyrocytes and OF. Secukinumab selectively inhibits the pro-inflammatory cytokine IL-17A. In the complex process of immunoreaction, IL-17A represents a 'fine tuning cytokine', enhancing the inflammatory processes. IL-17 activates tissue cells like OF, leading to an increased secretion of pro-inflammatory cytokines and infiltration of immune cells into the orbital tissue.

3.1 Efficacy of Batoclimab

In the recently performed Phase 2b IMVT-1401-2001 trial, Batoclimab dose-dependently reduced total IgG (30-60%) (191, 192). These results are consistent with other clinical trials evaluating the efficacy of Batoclimab in other indications like MG or neuromyelitis optica spectrum disorder (NMOSD) (193-196). The Batoclimab-induced reduction of total IgG levels is comparable to that of other FcRn inhibitors, e.g., Efgartigimod (60-85%), Nipocalimab (25-85%), Orilanolimab (50-58%), and Rozanolixizumab (24-80%) (122-124, 128-130, 197-201), all of which have been evaluated in the treatment of various IgG-mediated AID. Despite the reduction in IgG levels, clinical trials have also demonstrated a reduction in disease-specific aAb levels following Batoclimab treatment. Notably, the IMVT-1401-2001 trial is the first to report a depletion of EO-specific TSH-R-Ab. Reduction of IgG and TSH-R-Ab occurred rapidly after the first administration of the mAb. The nadir of the reduction was dose-dependent. After Batoclimab withdrawal, IgG and aAb levels spontaneously returned to baseline levels. This indicates both a dose-dependent and transient effect of Batoclimab.

The IgG reduction is comparable to the IgG reduction, achieved by plasmapheresis. In contrast to plasmapheresis, FcRn inhibition selectively reduces IgG levels without affecting other Ig isotypes such as IgA or IgM (202-206). Saturation and increased degradation of IgG like aAb can also be achieved with intravenous administration of IgGs (IVIG) of healthy donors. However, this treatment option is very expensive, and enormous amounts of healthy IgG are needed for one application, limiting the availability of IVIG as a standard of care option (59, 84, 85, 205, 206).

Compared with placebo, Batoclimab significantly improved the quality of life and inflammatory signs and symptoms of EO. At the primary endpoint, no significant improvements of exophthalmos or diplopia were observed. Due to the limited number of patients and early termination, the statistical power of the trial was reduced. Compared to placebo, in the treatment group, interim analysis showed improvements in both exophthalmos and diplopia. Further clinical trials with more robust statistical power are needed to evaluate the clinical efficacy of Batoclimab for the treatment of EO. Currently, Batoclimab is tested in two multicentric, double-masked, and placebo-controlled phase 3 trials in the treatment of EO.

3.2 Safety profile of Batoclimab

Overall, the treatment with Batoclimab was well tolerated. Only mild to moderate and transient AE were reported. The most frequent side effects in the IMVT-1401-2001 trial were: injection site reactions, fatigue, nausea, and peripheral edema (191, 207). This is consistent with the side effects reported in other clinical trials, evaluating Batoclimab in different indications (193-196). (193-196). The most common AE of other FcRn inhibitors, currently under clinical evaluation, are headache, gastrointestinal disorders (vomiting, nausea, and diarrhea), and pyrexia. It should be highlighted that peripheral edema was less frequently reported in the trial of the other FcRn inhibitors (122, 123, 127-130, 198, 199, 208). (122, 123, 127-130, 198, 199, 208). Under the treatment of the FcRn inhibitor Efgartigimod, bleeding events like petechial, purpura, blood in urine, and spontaneous bleeding of the gums were reported (124, 209). These AE did not occur in all Batoclimab trials.

The enhanced degradation of IgG may lead to an enhanced susceptibility to infection. In The ASCEND GO2 trial, no increased susceptibility to infection was observed in the Batoclimab group, in comparison to placebo. However, in two other clinical trials, an elevated number of urinary tract infections and infections of the upper respiratory tract were noted (194, 196). Similar results were reported in clinical trials of Efgartigimod (123, 125, 210), Nipocalimab (126, 198, 211), and Rozanolixizumab (129, 130, 212, 213). In the available literature, an increased susceptibility to infection after IgG degradation is discussed. Under physiological conditions, an IgG level above 500 mg/dl is necessary for sufficient immunoreaction. A reduction of IgG below 100 mg/dl is associated with a susceptibility to infections (112, 214). However, the IgG metabolism has no direct impact on the IgG synthesis. Independent of the IgG catabolism, the same amount of IgG is synthesized and secreted. Thus, a total eradication of IgG is unlikely (215-217).

Furthermore, the highly selective recycling mechanism of the FcRn only prolongs the half-life time of the IgG subclass. Other subclasses like IgA or IgM are not recycled by the FcRn. In line with this, no reduction of IgA or IgM was reported in the clinical trials, evaluating Batoclimab or another FcRn inhibitor. A complete immunosuppression under Batoclimab treatment is unlikely. This might be the most beneficial in comparison to other antibody-lowering options like plasmapheresis or BC depletion with Rituximab. Currently available Ab lowering treatment options impact all Ig subclasses and have no distinct effects on the Ig subclasses (202-204).

It should be kept in mind, that the clinical evaluation of FcRn inhibitors is affected by the coronavirus disease 2019 (COVID-19) pandemic. In numerous trials, COVID-19 infections were reported. However, there were no significant distinctions to placebo. In the IMVT-1401-2001 trial, an autoimmune-dependent encephalomyelitis occurred shortly after a COVID-19 infection of the patient. This SAE was not rated as drug related to Batoclimab. The pandemic might skew the safety profile of the FcRn inhibitors, especially regarding a potential enhanced susceptibility to infections.

A Batoclimab-related enhanced albumin clearance was noted in the IMVT-1401-2001 trial. Under physiological conditions, the amount of recycled albumin equivalent to the amount of new synthesized albumin (110, 218). Albumin is an important carrier protein for several apolar substances in the periphery. In the case of hypalbuminaemia, the body steers

against it by enhancing lipoprotein synthesis. This counteract of the body is not atypical. Patients with nephrotic syndrome (219-221) or congenital analbuminaemia (222-224) also have hypercholesterinemia. In both disorders, the low albumin level positively correlates with the increased levels of total cholesterol and LDL. The increase of lipoproteins on Batoclimab was also reported in the preclinical studies. Furthermore, hyperlipoproteinemia was observed in all clinical trials with Batoclimab. It should be highlighted that this phenomenon might be a substance class-specific side reaction. In patients treated with Nipocalmiab, or Rozanolixizumab, a transient albumin reduction was reported. However, in most cases, this reduction was mild and not clinically significant (126, 198-200, 213). The same applies to the increase of lipoproteins. In all cases the suppressed albumin titer and the increased level of lipoproteins normalized spontaneously after withdrawal of the drug. However, not all agents targeting the FcRn showed this effect. No albumin reduction was observed in patients treated with Efgartigimod. A recently published paper indicates that mAb targeting the FcRn cause FcRn degradation and interfere the albumin-FcRn interaction due to steric impairments (225).

Despite the increased risk of atherosclerotic events, hypercholesterinemia is a risk factor for EO. Patients with (active) EO have increased levels of both total cholesterol and LDL in comparison with healthy subjects (48, 49). A recent retrospective trial showed that patients with high levels of LDL respond less to IVGC treatment, compared with patients without hypercholesterinemia. Patients treated with both IVGC and statins had an enhanced response (226). Statins have shown beneficial anti-inflammatory effects in the treatment of RA and SLE. In the last few years, statins were also evaluated as potential treatment options for EO. Notably, the onset of EO in freshly diagnosed GD patients was reduced by 40% under statin treatment. This effect could not be achieved with other lipid-lowering drugs (227-229). The pleiotropic, anti-inflammatory effects of statins are not achieved through the LDL-lowering effect (228, 230-232). Statins (A) increase the apoptosis rate of macrophages, (B) enhance the autophagy, (C) enhance the tolerogenic DC differentiation, (D) inhibit the abiogenesis of OF, and (E) inhibit the OF differentiation into myofibroblasts. Furthermore, in animal models, statins showed an inhibiting effect of the IL-1β and IL-6 expression by TNF-α activated OF (228, 230-232).

The pharmacologic active form of a drug is represented by the unbound fraction of the drug, which is not bound to serum proteins (233-235). The most important carrier protein for drugs is albumin. Hypoalbuminemia can have a significant impact on the pharmacokinetics of a drug. At a constant dosage, hypoalbuminemia leads to a decrease in the bound fraction of the drug, while the total plasma concentration of the drug generally remains unchanged (233, 234, 236). A common misconception in the clinic is that the drug concentration decreases due to hypoalbuminemia, and the dosage must be increased. This misinterpretation of the pharmacokinetics may result in more frequent occurrence of side effects and intoxication. In case of hypoalbuminemia, dosages must be reduced (225, 233, 235).

This effect is particularly significant for drugs with a high plasma protein binding (≥ 90%) or a narrow therapeutic window, such as diazepam, valproic acid, phenytoin, and cyclosporin A. Continuous drug monitoring should be considered for patients on polymedication undergoing treatment with Batoclimab.

3.3 Efficacy of Secukinumab

The CAIN457ADE16 (ORBIT) trial was terminated prematurely due to low efficacy. Over the twelve-week treatment period, patients treated with Secukinumab showed no improvement in either proptosis or CAS. Only one patient in the Secukinumab group had an improvement of diplopia at the primary endpoint. Interestingly, the mAb showed a robust efficacy in treating psoriasis (PsO), psoriatic arthritis (PsA), and ankylosing spondylitis (AS). In these indications, a significant, rapid, and persistent improvement was reported in the clinical trials. It is worth noting that Secukinumab has been tested for several other AID with heterogeneous results (237-240). Experimental studies revealed an involvement of IL-17 in the pathogenesis of various AID, including SLE and lupus nephritis (LN) (241, 242). Furthermore, there are case reports of patients with SLE or LN who experienced an improvement in clinical signs and symptoms following treatment with Secukinumab (243, 244). A phase 3 trial with an open-label extension for the treatment of LN was terminated prematurely. The trial was terminated by the Sponsor due to the lack of efficacy of Secukinumab, compared with placebo (245, 246). Both SLE and EO are aAb-mediated AID. PsO, PsA, and AS are predominantly TC cytokine-mediated AID. IL-17 has a different pathogenetic dominance in these diseases. IL-17 might play a primarily immunomodulatory role in the pathogenesis of EO, as suggested by the lack of efficacy observed with IL-17 inhibition. TSH-R-Ab activating OF induces the expression of pro-inflammatory cytokines (e.g., IL-6), chemokines, and adhesion molecules. IL-6 has an autocrine effect on Th17 TC. Furthermore, chemokines and adhesion molecules increase the infiltration of immune cells in the orbital tissue and enhance the local inflammation.

Cytokine-induced interaction between immune cells themselves or tissue cells is an intricate, regulatory network. Inhibition of a specific cytokine or signalling pathway can be compensated for by an increased expression of another cytokine. This is partly because cytokines exert differentiating or suppressive effects on specific TC subsets, thereby influencing the cytokine balance. Chronic inflammation is often characterized by a dysregulation between pro- and anti-inflammatory cytokines. Despite this imbalance, a different balance between the cytokines might be present and maintain the chronic inflammatory state. An inhibition of one or more cytokines can also cause a shift in the balance and cause an inflammatory episode. This paradoxical phenomenon cannot be completely excluded from the EO. The magnitude of a cell, reacting to a cytokine, depends on several factors (A) receptor expression and density, (B) cell number, and (C) accessibility of the tissue for both cells and cytokines. Organ-specific differences in IL-17 sensitivity between EO compared to PsO, PsA, and AS cannot be excluded. IL-17R expression on OF of EO patients and healthy controls was demonstrated. EO OF expresses significantly more IL-17R compared to healthy controls. However, there is no direct comparison between OF and keratinocytes or synovial fibroblasts. To exclude a tissue or organ-specific sensitivity, afore mentioned cells should be compared directly.

Also, disease-specific aspects affecting the pharmacokinetics of Secukinumab should be considered. The increased volume of the orbital tissue causes a stenosis of orbital lymphatic and blood vessels. This might affect the distribution of Secukinumab into the orbital tissue. Experimental trials have demonstrated a distinct presence of both Th17 TC and IL-17 in the orbital tissue of EO patients. A limited, local availability of the mAb might explain the observed lack of efficacy. No disease-specific factors, limiting drug distribution,

are reported or discussed for PsO, PsA, or AS. To confirm or exclude the potential limited drug availability of Secukinumab in the orbital tissue, further investigations with higher doses are needed.

3.4 Safety profile of Secukinumab

The safety of Secukinumab has been demonstrated in several clinical trials and post-marketing analyses for the indications PsO, PsA, and AS. Data from the last two decades has been discussed in several reviews (237, 239, 240, 247-249). Secukinumab showed a great safety profile in all trials. Occurred AE were mild-moderate and transient. This applies both to short-term use and to treatment periods exceeding five years (247-249). The most common events were: Headache, diarrhea, infusion-/injection site reactions nasopharyngitis, upper respiratory tract infections, and candida infections (237, 239, 247). In line with the exceed safety results, AE in the CAIN457ADE trial were mild-moderate. Only two SAE occurred (one in each group), related to the intervention. Injection site reactions occurred rarely and did not differ in quantity and severity between the two groups.

Conditioned by the physiologic function of IL-17 against pathogens, an increased susceptibility to infection and malignancy was discussed. Neither the ORBIT trial nor the comprehensive safety reviews could prove an increased susceptibility or a trend for both, infections and malignoma. During the ORBIT trial, one case of malignant tumor was reported by a patient, treated with Secukinumab. In contrast to TNF-α inhibitors, IL-17 inhibiting mAbs like Secukinumab does not increase the risk of malignancy (237, 247, 248). Under physiological conditions, IL-17 increases the signal transducer and activator of transcription 3 (STAT3) dependent β-defensine expression. Defensines are an important factor in protecting the body against fungi and parasites. Animal models with STAT3 deficient mice showed an increased susceptibility to infection, mainly fungal infections (161, 168, 250). In the ORBIT study, treatment with Secukinumab was not associated with an increased incidence of infections compared to placebo. Only one patient treated with Secukinumab reported oral candidiasis. The most frequently reported infection in both groups was COVID-19 (four cases in the Secukinumab and six cases in the placebo group). Under consideration of the unusual conditions of the pandemic and the comparable prevalence of the groups, it seems unlikely that Secukinumab increased susceptibility to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Furthermore, no increased susceptibility to opportunistic infections was reported in clinical trials and post-marketing analyses (239, 247-249).

In rare cases, mild and transient neutropenia was reported by patients, treated with Secukinumab. During the CAIN457ADE16 trial, one case of neutropenia occurred in the mAb group. Further rare but severe potential side effects of IL-17 inhibitors are the development of drug-induced systemic lupus or inflammatory bowel disease (IBD) (240, 247, 249). Neither Secukinumab-induced systemic lupus nor IBD was reported during the ORBIT trial. It should be mentioned that patients with known active IBD were excluded from the trial. A potential worsening of IBD could not be evaluated in this trial. In a recent phase 3 trial, IBD patients were treated with either Secukinumab or placebo. The trial was terminated prematurely by the sponsor due to (A) lack of efficacy in comparison to placebo and (B) worsening of the IBD under treatment with Secukinumab. In summary, the

monoclonal antibody Secukinumab demonstrated an excellent safety profile in the CAIN457ADE study, consistent with previously published data.

3.5 Future perspectives and concluding remarks

In clinical trials, Batoclimab has been shown to have beneficial and promising effects in the treatment of IgG-mediated AID, as EO. In the early, active phase of EO, the mAb significantly reduced the inflammatory signs and symptoms, compared to placebo. This effect emphasizes a potential role for Batoclimab in the early stage of EO. No significant effect on orbital tissue remodeling (e.g. diplopia or exophthalmos) compared to placebo was shown in the ASCEND GO2 trial. More trials with an increased number of EO patients are needed to evaluate the effect of Batoclimab on tissue remodeling or the late stage of EO. Despite the effect on inflammatory signs and symptoms, Batoclimab also has shown a beneficial effect on the metabolic state of the thyroid. A recent monocentric trial is evaluating the potential use of Batoclimab for the treatment of GD patients. Data from an interim analysis show promising effects of the mAb. The standard of care antithyroid treatment could be reduced or withdrawn in most of the patients. In addition, Batoclimab demonstrated a safety profile consistent with that observed in previously conducted clinical trials.

A recent phase I trial evaluated the concomitant application of Batoclimab and atorvastatin (251). No influence of the pharmacokinetics and pharmacodynamics was observed for Batoclimab or atorvastatin. Statins like atorvastatin could prevent an FcRn inhibitor-mediated increase of lipoproteins. Furthermore, the anti-inflammatory and anti-proliferative effects of statins on fibroblasts could synergistically interact with the aAb reduction of Batoclimab. However, a potential influence of the cytochrome-p450 (CYP) enzyme induction of statins could be evaluated, especially in multimorbid patients or patients on polymedication.

TSH-R-Ab are of the IgG subtype and can cross the placenta barrier into the fetal bloodstream in pregnant women (252-254). This transcytosis is possible due to the expression of FcRn in the syncytiotrophoblast (78, 83, 84, 255). The transcytosis of IgG and aAb starts in the 13th week of pregnancy (252). During pregnancy, aAb levels in the fetal bloodstream can increase up to 50 % of the maternal levels. Furthermore, the transcytosis rate increases with the progression of the pregnancy (253). The development of the fetal thyroid starts in the 20th week of pregnancy. TSAb, as well as TBAb, can directly impact the cognitive and physical development of the fetus (253). Therefore, close monitoring of the TSH-R-Ab during pregnancy is warranted. Anti-thyroid treatment can be continued during pregnancy under close monitoring, although thionamide antithyroid drugs (ATD) cross the placenta barrier, and a teratogenic effect of thioamides has been reported (252, 253, 256). Inhibition of the FcRn during pregnancy was investigated in animal models for the aAb-mediated AIDs neonatal alloimmune thrombocytopenia (257) and arthrogryposis multiplex congenital (258). FcRn inhibition resulted in a significant decrease of aAb in the fetal bloodstream.

The first clinical trial to investigate FcRn blockade in pregnant women was conducted using Nipocalimab in patients with hemolytic disease of the fetus and newborn (200, 259). In this open-label phase 2 trial, 54% of the women responded to treatment (healthy child without blood infusion), and aAb levels in the fetal bloodstream were significantly reduced. Treatment with Nipocalimab was well tolerated. Neither the newborn nor the mother

experienced a severe infection. No increased number of premature births or cognitive/physical impairments of the newborn were reported. Inhibition of the FcRn in pregnant women with IgG aAb-mediated AID could be a new and promising treatment option. Currently, there is no data on FcRn inhibition in pregnant women with GD or EO available, nor are studies planned for these indications. However, it must be taken into account that data from animal models cannot be transferred 1:1 to humans, due to differences in the FcRn. Furthermore, clinical trials involving pregnant women are very ethically challenging.

The contribution of Th17 TC and IL-17 to the pathogenesis of the EO were experimentally verified in sera and tissue of patients by several independent groups. The inhibition of IL-17 by Secukinumab, unfortunately, showed no beneficial effects in the CAIN457ADE16 (ORBIT) trial. However, IL-17 should not be overlooked as a potential therapeutic target for treatment. Recent experimental trials with the peroxisome proliferator-activated receptor gamma (PPARγ) agonist Fenofibrate showed an inhibitory effect on the adipogenesis of OF and also a robust suppression of Th17 TC. The underlying mechanism is not fully understood and needs to be evaluated further. This inhibitory effect on Th17 TC and indirect on IL-17, combined with the suppression of adipogenesis, could be another target for treating EO. Furthermore, the indirect effect of IL-23 inhibition on IL-17 should also be evaluated. Recent in vitro studies also evaluated small molecules against the key transcription factor of IL-17, retinoid orphan receptor gamma t (RORγt). This may also represent a promising therapeutic target by suppressing the pro-inflammatory effects of IL-17 and Th17 TC at an additional regulatory level. Due to the lack of efficacy and the premature termination of the ORBIT trial, Secukinumab will not be further investigated or licensed for the treatment of EO.

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STATUTORY DECLARATION

I hereby declare that this PhD dissertation entitled "*SAFETY AND EFFICACY OF NOVEL MONOCLONAL ANTIBODIES FOR ENDOCRINE ORBITOPATHY*", is my own independent work. I have only used given sources, results and material and I have cited others' work appropriately.

Mainz, _____

Jan Wolf

CURRICULUM VITAE

- Removed from the electronic version for data protection reasons -

CONDUCTED CLINICAL TRIALS

- A randomized, double-masked, controlled, safety and tolerability study of VRDN-003 in participants with thyroid eye disease (TED) (**VRDN-003-303**)

- A Phase 3, Multi-center, Randomized, Quadruple-masked, Placebo-controlled Study of Batoclimab for the Treatment of Participants with Active Thyroid Eye Disease (TED) (**IMVT-1401-3202**)

- A randomized, controlled, safety and tolerability study of VRDN-001, a humanized monoclonal antibody directed against the IGF-1 receptor, in participants with thyroid eye disease (TED) (**VRDN-001-303**)

- A Phase 3, Multi-center, Randomized, Quadruple-masked, Placebo-controlled Study of Batoclimab for the Treatment of Participants with Active Thyroid Eye Disease (TED) (**IMVT-1401-3201**)

- A Proof-of-Concept, Open-label Study to Assess the Safety and Efficacy of Batoclimab in Participants with Graves' Disease (GD) (**IMVT-1401-2501**)

- A Phase 3b/4, Double-masked, Randomized, International, Parallel-assignment, Multicenter Trial in Patients with Thyroid Eye Disease to Evaluate the Safety and Tolerability of Different Dosing Durations of Teprotumumab (**HZNP-TEP-402**)

- A two-year multi-center Phase 3 study to investigate the efficacy and safety of secukinumab in adult patients with active, moderate to severe thyroid eye disease (ORBIT), with a randomized, parallel-group, double-blind, placebo-controlled, 16-week treatment period, and a follow-up/retreatment period (**CAIN457ADE16**)

- ASCEND GO 2: A Phase 2b, Multicenter, Randomized, Double-blind, Placebo-controlled Study of RVT-1401 for the Treatment of Patients with Active, Moderate to Severe Graves' Ophthalmopathy (**RVT-1401-2001**)

PUBLICATIONS AND CONTRIBUTIONS

Publications as first author

- Safety and tolerability of anti-FcRn monoclonal antibody in thyroid autoimmunity. Exploration of Immunology 2024, **J. Wolf**, I. Krämer, G. J. Kahaly
- A Novel Monoclonal Antibody Degrades the Thyrotropin Receptor Autoantibodies in Graves Disease. Endocr Pract 2023, **J. Wolf**, S. Alt, I. Kramer, G. J. Kahaly
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Publications as co-author

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