Sling Therapeutics

Linsitinib Oral Treatment Option for Thyroid Eye Disease

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Sling Highlights

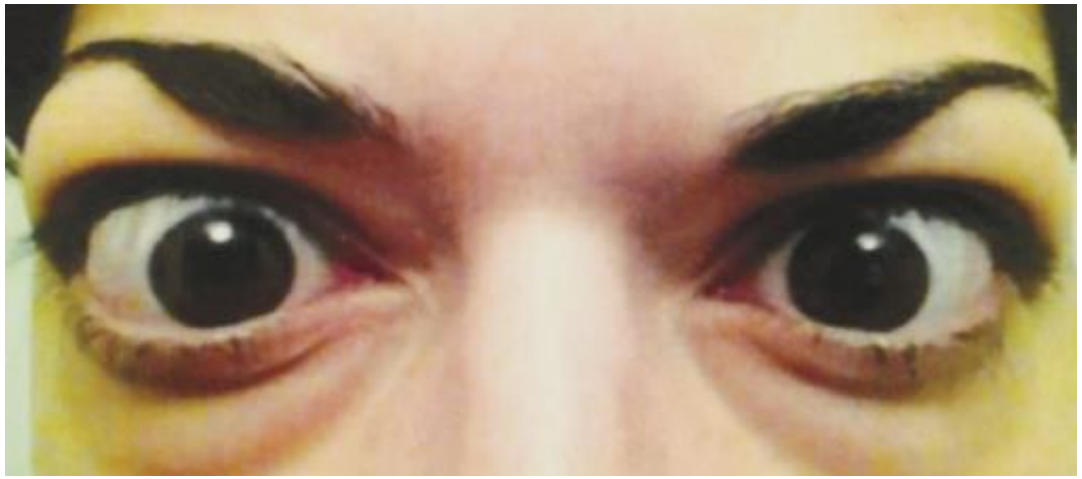
Linsitinib is a convenient oral therapy and with positive Phase 2b/3 TED data establishing IGF-1R efficacy and a differentiated safety profile

- Positive Phase 2b/3 study statistically significant and clinically meaningful proptosis reduction
- Differentiated safety profile with no drug-related hearing impairment or significant hyperglycemia
- Only oral therapy in clinical trials for TED, avoiding infusions and reducing barriers to use for physicians and patients
- Favorable safety profile with 900+ patients treated
- Private and highly capital efficient biotech
- Optimized, high-yield CMC process with long shelf-life
- TED is a multi-billion-dollar market opportunity
- Series B financing completed Jan 2024

Linsitinib's clinical profile and convenience could create a new TED treatment option for a broader number of physicians across multiple therapeutic disciplines and reduce patient hurdles to treatment

CMC, chemistry, manufacturing, and controls; IGF-1R, insulin-like growth factor 1 receptor; PK/PD, pharmacokinetics/pharmacodynamics; TED, thyroid eye disease.

TED is a Rare and Debilitating Eye Disease



Estimated ~70,000 TED patients in US[1]

Similar prevalence in EU

Focusing on a serious progressive ocular autoimmune condition

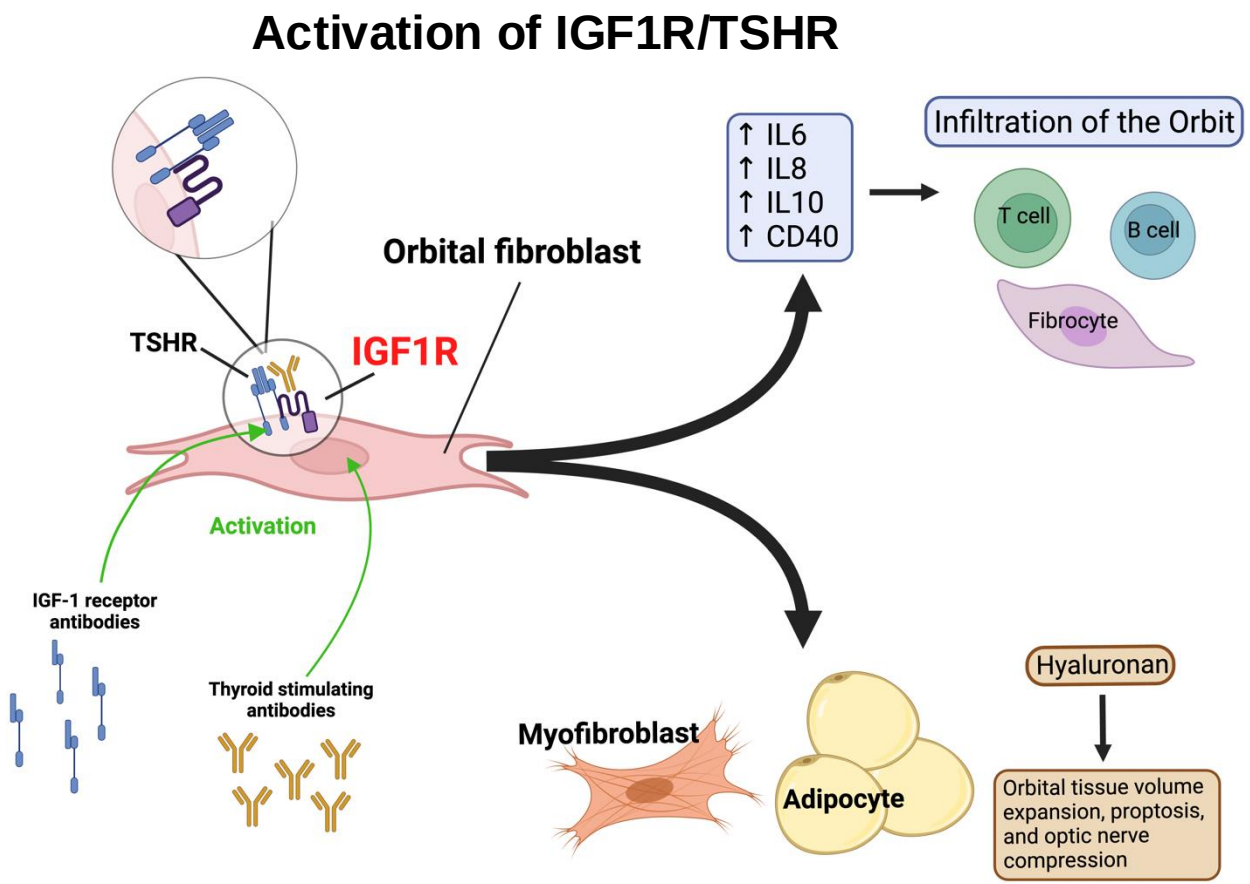
A subset of Graves' disease, TED is driven stimulation of IGF-1R fibroblasts behind the eye[2]

Symptoms include disfiguring proptosis (eye bulging), double vision, pain, and potentially profound reduction in quality of life[3]

TED, thyroid eye disease.

1. Chen X, et al. ATA Annual Meeting, Washington, DC, 27 September–1 October 2023. Poster 523; 2. Shu X, et al. *Front Immunol.* 2024;15:1392956; 3. Rashad R, et al. *Life (Basel).* 2022;12(12):2084.

IGF-1R is Central to the Pathogenesis of TED and Inhibition Has Been Shown to Improve the Disease

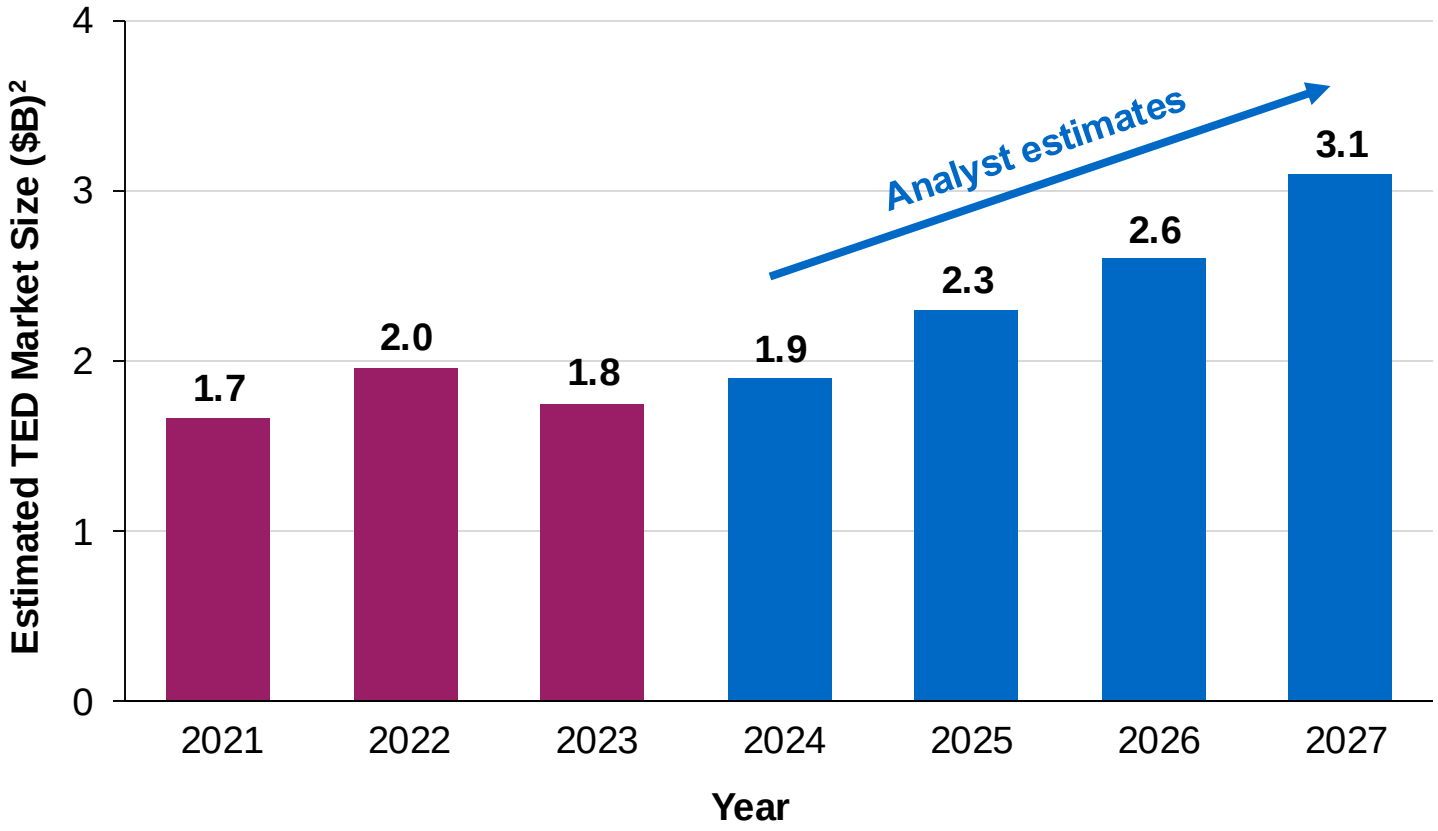


- IGF-1R pathway is believed to be the main biological driver of TED
- IGF-1R is upstream of other pathways being investigated as potential TED treatments
- Numerous IGF-1R inhibitors have been shown to be effective at treating TED

CD, cluster of differentiation; IGF-1R, insulin-like growth factor 1 receptor; IL, interleukin; TED, thyroid eye disease; TSHR, thyroid-stimulating hormone receptor.

TED is a Large Market That is Expected to Grow

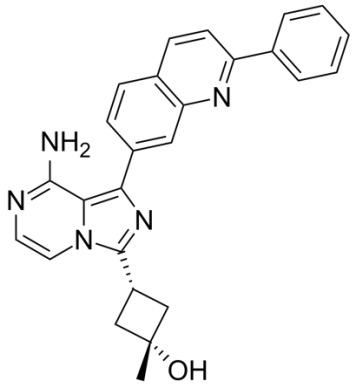
- Only approved TED therapy generates ~$2B[1] in revenue and has been a very successful rare disease launch
- Small portion of ~70,000 TED patients currently receive therapy each year
- Growth has been restricted primarily by limited physician prescriber base, inconvenience, and concerns with side effects



TED, thyroid eye disease.
1. Tepezza sales figures from Horizon (now Amgen) reports; 2.Various sales forecasts and consensus estimates.

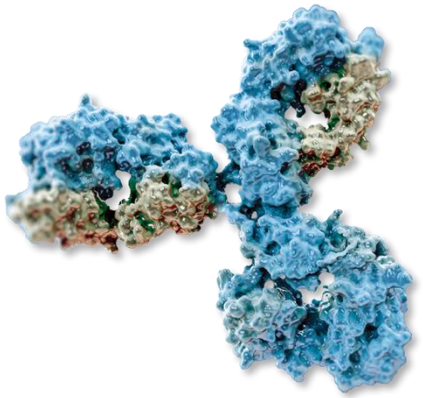
Linsitinib is the Only Orally-Administered Small Molecule Drug in Clinical Trials for TED

Linsitinib is an Oral Small Molecule



- Low molecular weight (~400 daltons)
- No refrigeration needed
- Formulated as standard tablets for dosing
- Short half-life with ~1 day wash-out period

Monoclonal Antibodies are Injected

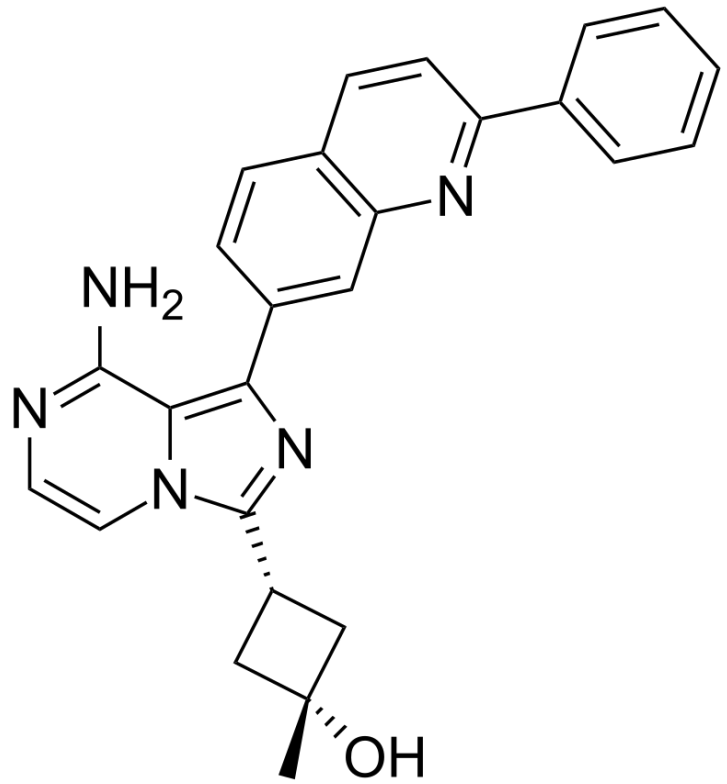


- High molecular weight (150,000+ daltons)
- Refrigeration required
- Re-constitution / dilution at point of administration for IV products
- Long half-life with month+ washout period

IV, intravenous; TED, thyroid eye disease.

Linsitinib Manufacturing is Simple and Well Established with Long Shelf Life

Linsitinib



- Three-step synthesis of API with known, reproducible chemistry, high yields and purity
- Produced at 20+ kg scale at multiple vendors
- Exceptional shelf-life (4 years) at room temperature to support commercial launch
- Low cost and complexity of manufacturing

API, active pharmaceutical ingredients; BID, twice daily.

Linsitinib is the Only Oral, Small Molecule Treatment Under Development for TED

Asset	Target	Route	TED stage of development
Tepezza[1,2]	IGF-1R	IV	Approved
Linsitinib[1,3]	IGF-1R	**Oral**	Phase 3
VRDN001 and 003[1,4]	IGF-1R	IV/SC	Phase 3
Satralizumab[1,5]	IL-6	SC	Phase 3
Batoclimab[1]	FcRn	IV	Phase 3
Efgartigimod[1]	FcRn	IV/SC	Phase 3
TOUR006[1]	IL-6	SC	Phase 2
LASN01[6]	IL-11R	IV	Phase 2
Lonigutamab[1]	IGF-1R	SC	Phase 2

Disclosed trials/drugs as of December 5, 2024. FcRn, neonatal fragment crystallizable receptor; IGF-1R, insulin-like growth factor 1 receptor; IL, interleukin; IV, intravenous; SC, subcutaneous; TED, thyroid eye disease; TSHR, thyroid-stimulating hormone receptor.

1. Park JW, Yoon JS. *Korean J Ophthalmol*. 2024;38(3):249-259; 2. Nie T, Lamb YN. *Drugs*. 2022;82(17):1663-1670; 3. NCT05276063. CTgov. https://clinicaltrials.gov/study/NCT05276063. Accessed August 2024; 4. Thyroid Eye Disease Programs. Viridian. https://www.viridiantherapeutics.com/pipeline/ted-programs/. Accessed August 2024; 5. NCT05987423. CTgov. https://clinicaltrials.gov/study/NCT05987423. Accessed August 2024; 6. NCT05331300. CTgov. https://clinicaltrials.gov/study/NCT05331300. Accessed August 2024.

Sling is Establishing a Scientific Leadership Role in IGF-1R Pathway Biology and TED with World Leading TED KOLs

Dr. Anja Eckstein

- Head of Department of Oculoplastic and Reconstructive Surgery
- Head of the Orbital Care Center for TED at Essen
- Evaluated and published mouse model demonstrating linsitinib biological activity

Dr. George Kahaly

- Prof. of Medicine and Endocrinology at Johannes Gutenberg University
- World renowned TED KOL and leading scientist and researcher
- Evaluated and published effect of linsitinib on TED cell apoptosis

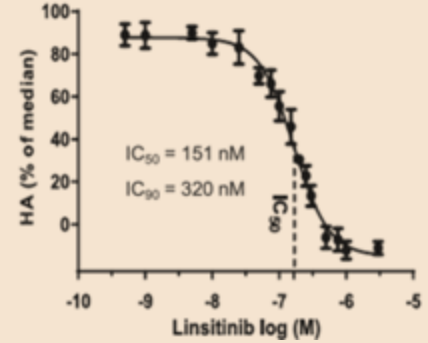
Sling is widely engaging the scientific community and supporting efforts to maximize the understanding of TED and IGF-1R inhibition

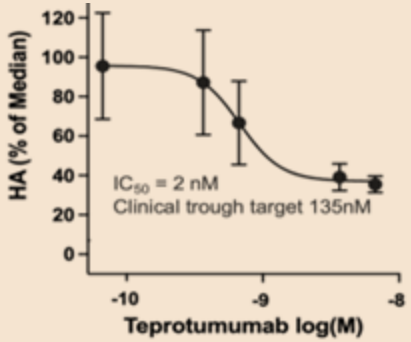
IGF-1R, insulin-like growth factor 1 receptor; KOL, key opinion leader; TED, thyroid eye disease.

Growing Scientific Body of Evidence Supporting Linsitinib's Ability to Inhibit IGF-1R to Treat TED

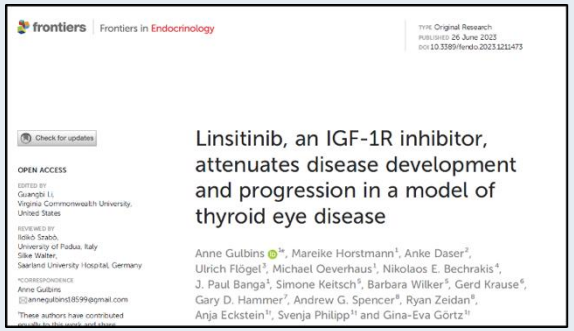
Linsitinib inhibits human fibroblast cell hyaluronan production

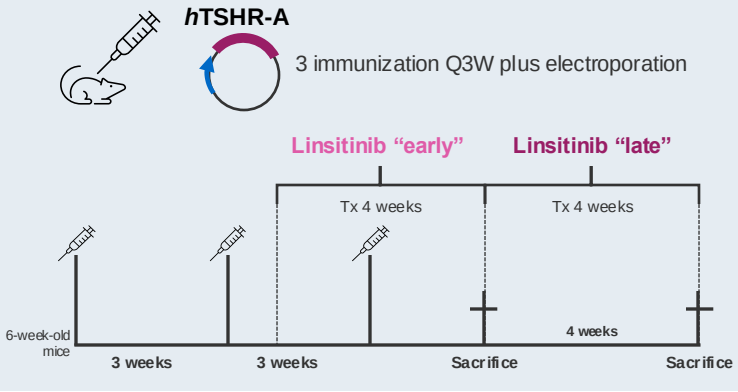
Linsitinib and teprotumumab in human Graves' orbital fibroblast model[a]





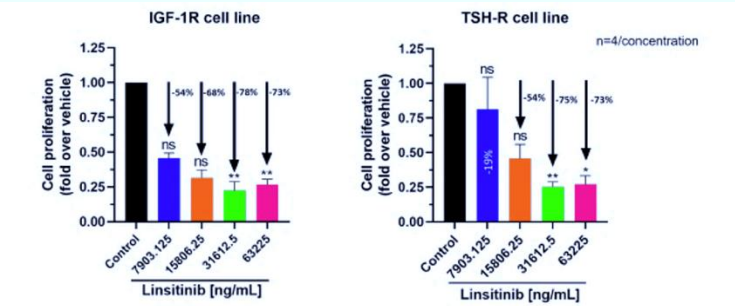
Linsitinib prevents and treats TED in a disease mouse model[1]



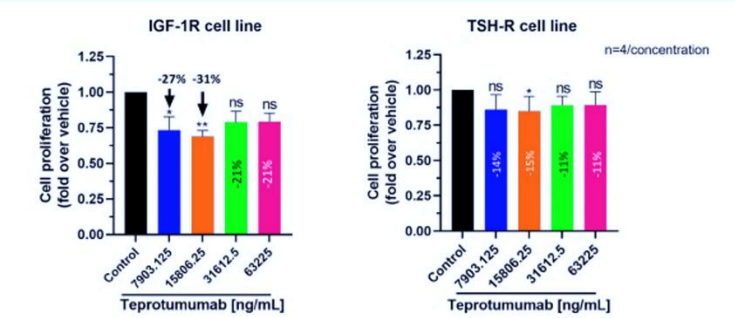


Linsitinib inhibits proliferation and induces apoptosis of IGF-1R expressing cells[2]

Proliferation assay: Linsitinib



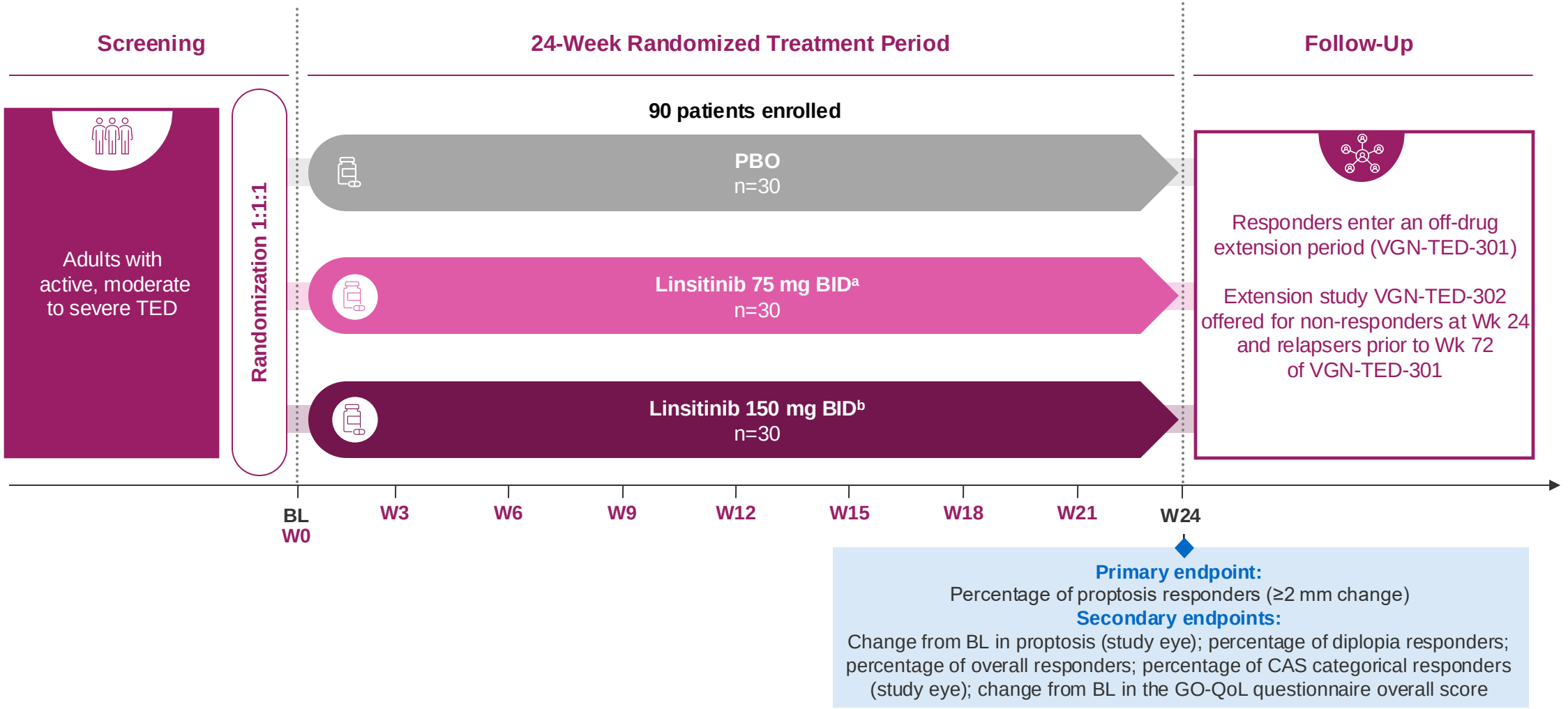
Proliferation assay: Teprotumumab



[a]Tepezza data were replotted in Prism® from data published in Krieger, 2021 to adjust y-axis units to match those from the linsitinib data in Place, et al., 2017. Experiments are performed in the presence of serum.
*h*TSHR, human thyrotropin receptor; IC50, half maximal inhibitory concentration; IGF-1R, insulin-like growth factor 1 receptor; Q3W, every 3 weeks; Tx, treatment; TED, thyroid eye disease; TSH-R, thyroid-stimulating hormone receptor.

1. Gulbins A, et al. *Front Endocrinol (Lausanne).* 2023;14:1211473; 2. Luffy M, et al. *Front Immunol.* 2024;15:1488220 [Epub ahead of print].

LIDS is a Randomized, Double-Masked, Placebo-Controlled Phase 2b/3 Trial



[a]75 mg BID dose to assess the minimally effective dose in TED; [b]150 mg BID dose safely studied in multiple oncology clinical trials. Phase 2b/3 trial includes many TED KOLs at 35 sites across US, Canada, UK, Italy, Spain.
BID, twice daily; BL, baseline; CAS, clinical activity score; GO-QoL, Graves' ophthalmopathy quality of life; PBO, placebo; TED, thyroid eye disease; Wk, week.
Sling Therapeutics. Data on File.

Key Criteria for Patient Eligibility

Key Inclusion Criteria

- 18 years of age or above
- **Clinical diagnosis of Graves' disease and/or autoimmune Hashimoto's thyroiditis associated with active moderate to severe TED with CAS score ≥4 in at least one eye**
- **Confirmed active moderate to severe TED diagnosis within the last 12 months**
- Do not require immediate ophthalmic surgery, radiotherapy to orbits or other ophthalmological intervention (prior cataract surgery or LASIK >3 months ago is not exclusionary)
- Euthyroid with baseline disease under control or have mild hypo- or hyperthyroidism at screening

Key Exclusion Criteria

- Previous orbital irradiation or surgery
- Prior IGF-1R inhibitor therapy for any condition
- Malignant conditions being actively treated or treated in the past 12 months (with the exception of successfully treated basal cell of the skin); recent (within 3 months of screening) basal cell of the eyelid skin is excluded
- Pregnant or lactating women

CAS, clinical activity score; IGF-1R, insulin-like growth factor 1 receptor; LASIK, laser-assisted in situ keratomileusis; TED, thyroid eye disease.
Sling Therapeutics. Data on file.

LIDS Phase 2b/3 Study Designed as a Robust Pivotal Study with Numerous Clinical Endpoints

Study Procedures

- CAS
- CSS including proptosis, motility, diplopia
- GO-QoL questionnaire
- Hyperglycemia evaluation
- ECGs in triplicate
- Eye exams
- Physical exams with vital signs
- Laboratory tests
- Pharmacokinetic assessments
- Pharmacodynamics assessments
- Adverse events, serious adverse events

BL, baseline; CAS, Clinical Severity Score; CSS, Clinical Severity Score; ECG, electrocardiogram; GO-QoL, Graves' ophthalmopathy quality of life.
Sling Therapeutics. Data on file.

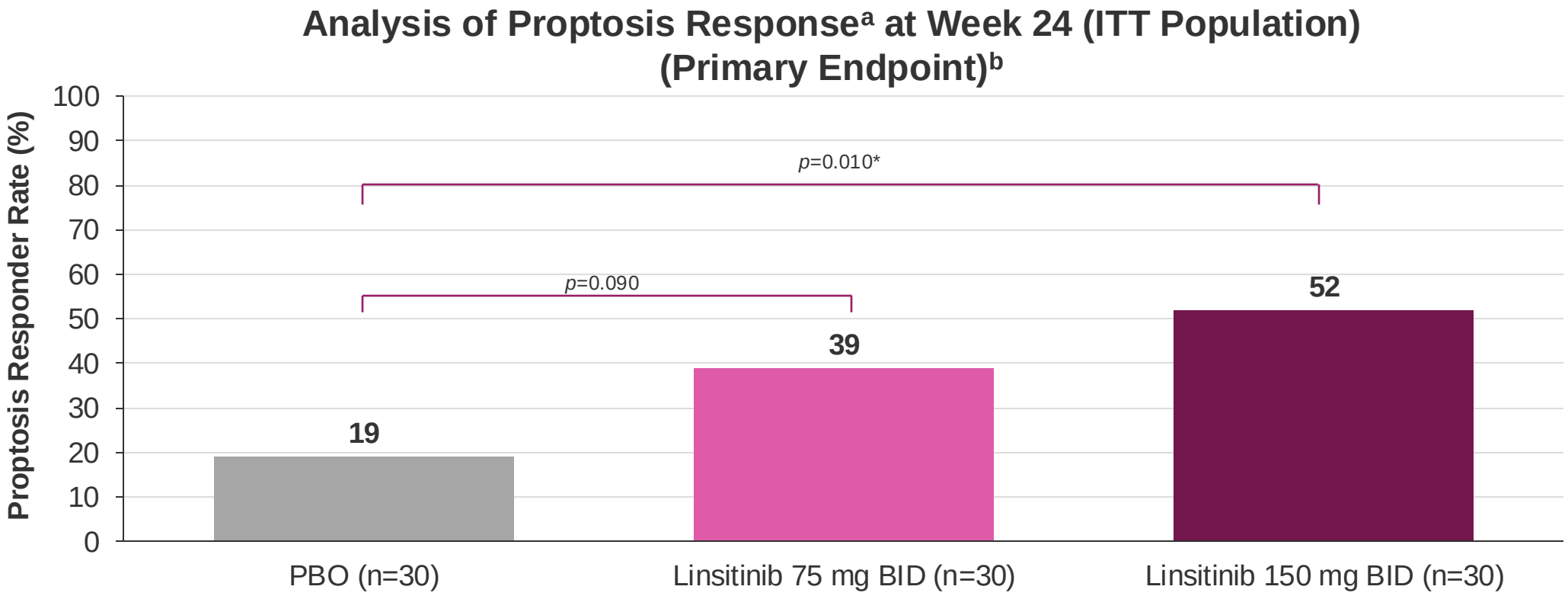
Global Study with 35 Sites Participating from US, Canada, UK and EU

Baseline Demographics and Patient Characteristics

Characteristic	PBO n=30	Linsitinib 75 mg BID n=30	Linsitinib 150 mg BID n=30
Age (years), mean (SD)	50.9	52.8	50.1
Female %	56.7	63.3	70
Race			
White %	86.7	83.3	76.7
Black %	6.7	10	10
Asian %	6.7	3.3	13.3
Other	0.0	0.0	0.0
Smoker %	16.7	36.7	6.7
Proptosis (mm), mean (SD)	23.8	23.0	22.0

BID, twice daily; PBO, placebo; SD, standard deviation; TED, thyroid eye disease.
Sling Therapeutics. Data on File.

Proptosis Responder Rate Primary Endpoint Was Statistically Significant for the 150 mg BID Dose

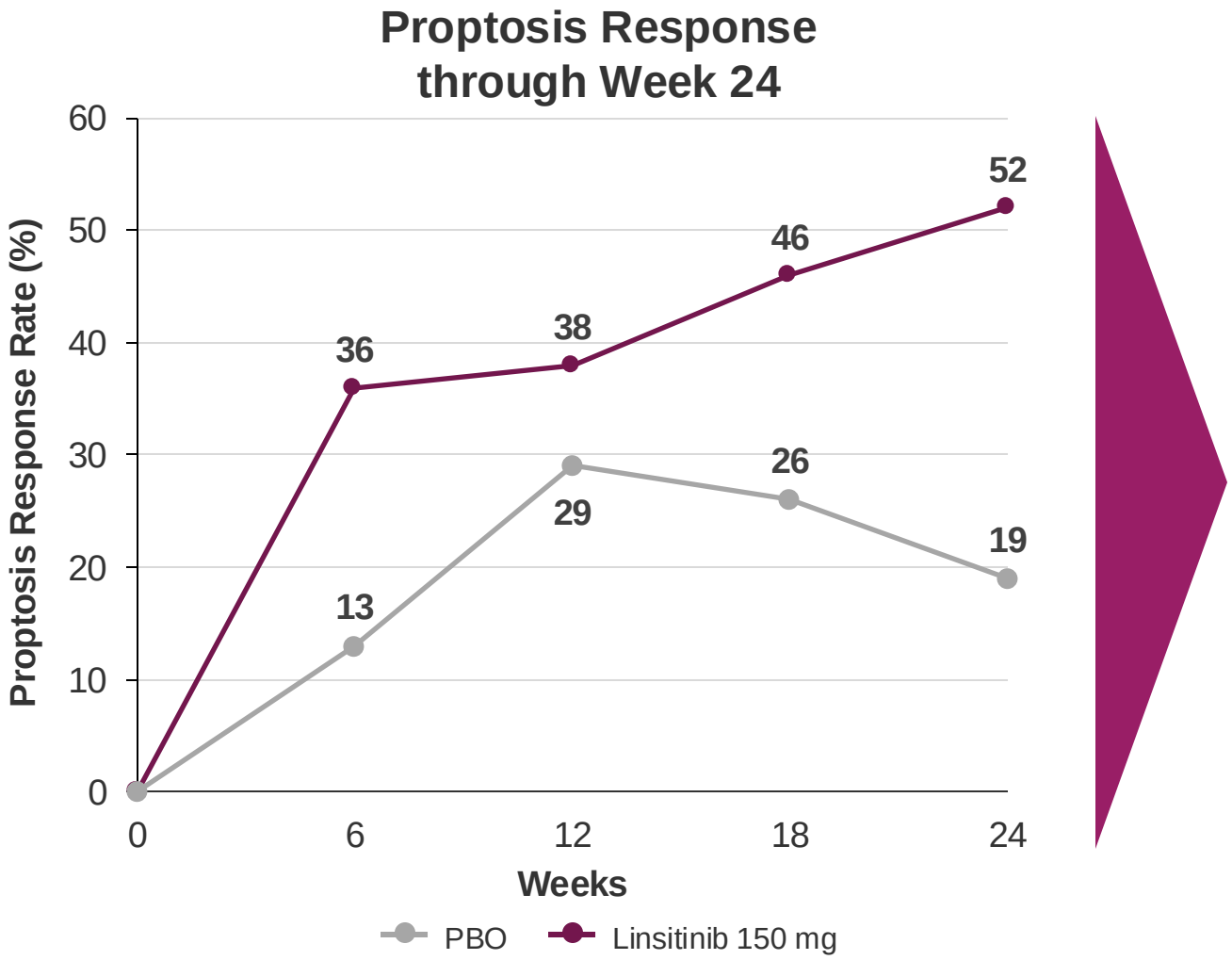


[a]≥2 mm reduction from BL in the primary study eye without deterioration (≥2 mm increase) of proptosis in the contralateral non-study eye; [b]Based upon a CMH test, stratified by smoking status at a one-sided significance level α=2.5%. *P*-value is based upon transformed Wilson-Hilferty CMH test statistic. Following Hochberg testing rules, if the larger *p*-value (regardless of dose) is <0.025 then both doses are considered statistically significant from PBO. If the larger *p*-value is ≥0.025 then this dose is not considered statistically significant and then smaller p-value is evaluated at α=0.0125. If *p*-value is <0.0125 then this dose is considered statistically significant from PBO (indicated by *).

BID, twice daily; BL, baseline; CI, confidence interval; CMH, Cochran-Mantel-Haenszel; ITT, intent to treat; PBO, placebo; SE, standard error.

Sling Therapeutics. Data on File.

Linsitinib Responders Show Response Early in the Treatment Course and Continue to Respond Through 24 Weeks

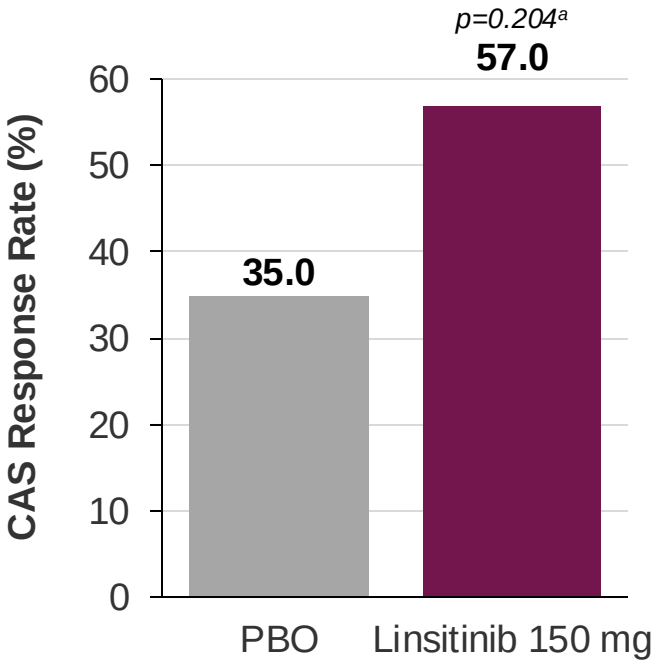


- Majority of responders (~70%) show response by Week 6
- Increasing response rate through Week 24
- High placebo response driven by low n (4 out of 25 patients at Week 24)
- Clear and statistically significant separation from placebo at Week 24

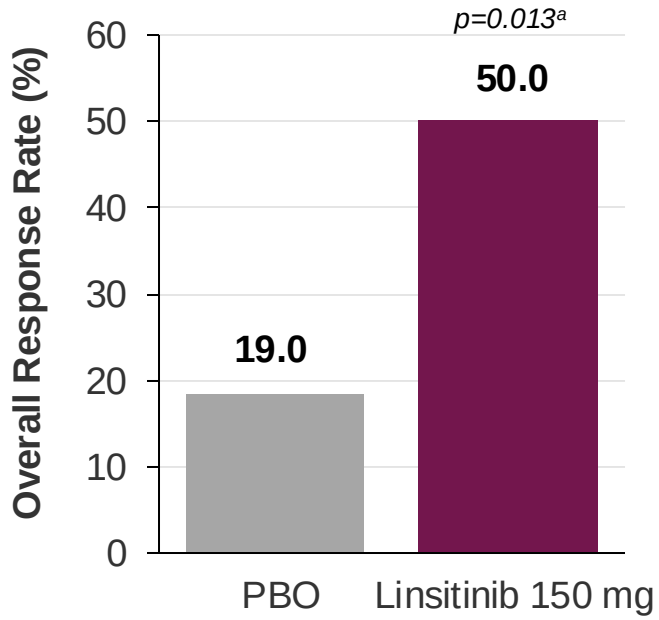
PBO, placebo.
Sling Therapeutics. Data on File.

Key Secondary Endpoints Showed Numerical Clinically Meaningful Improvement

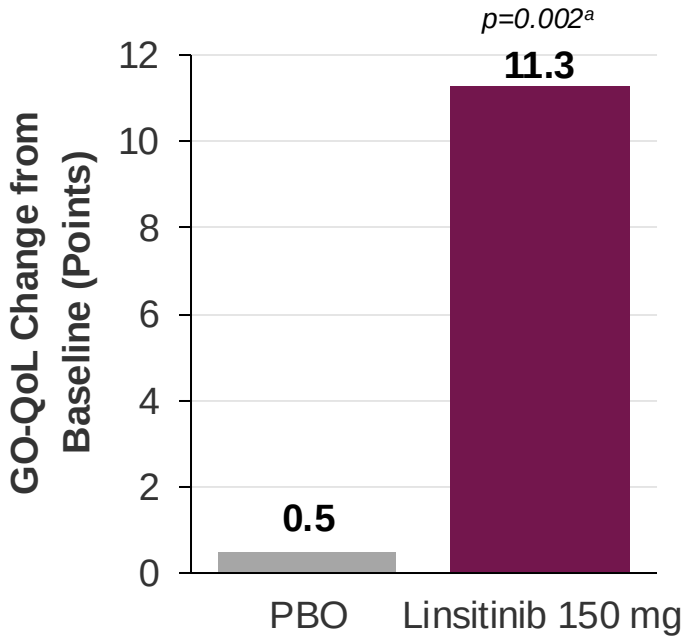
CAS Response at Week 24



Overall Response at Week 24



Change in GO-QoL at Week 24



Magnitude of drug effect on secondary endpoints similar to other IGF-1R therapies

[a]Confirmatory statistical testing not performed on secondary endpoints due to hierarchical procedures
CAS, clinical activity score; GO-QoL, Graves' ophthalmopathy quality of life; IGF-1R, insulin-like growth factor 1 receptor; PBO, placebo.
Sling Therapeutics. Data on File.

Summary of Treatment-Emergent Adverse Events

TEAEs	PBO n=31 n (%)	Linsitinib 75 mg BID n=30 n (%)	Linsitinib 150 mg BID n=29 n (%)
TEAE of any grade	22 (71.0)	21 (70.0)	23 (79.3)
TEAE considered possibly related	9 (29.0)	13 (43.3)	16 (55.2)
TEAE leading to study drug discontinuation			
Any	2 (6.5)	5 (16.7)	9 (31.0)
SAE			
Any	1 (3.2)	0 (0.0)	2 (6.9)
AE leading to death	0 (0.0)	0 (0.0)	0 (0.0)

Patients in VGN-TED-301 were randomized to receive PBO (n=30), linsitinib 75 mg (n=30) or linsitinib 150 mg (n=30); the primary endpoint was the percentage of proptosis responders (≥2 mm change) at Week 24.
One subject from the linsitinib 150 mg BID arm was mis-randomized to placebo and has been included as part of the placebo group for all safety assessments.
AE, adverse event; BID, twice daily; PBO, placebo; SAE, serious adverse event; TEAE, treatment emergent adverse event.
Sling Therapeutics. Data on File.

Treatment-Emergent AEs >10% in Any Treatment Group

Any TEAE >10% in any treatment group	PBO n=31 n (%)	Linsitinib 75 mg BID n=30 n (%)	Linsitinib 150 mg BID n=29 n (%)
Diarrhea	2 (6.5)	4 (13.3)	6 (20.7)
Headache	1 (3.2)	3 (10.0)	6 (20.7)
Nausea	1 (3.2)	3 (10.0)	6 (20.7)
Fatigue	2 (6.5)	5 (16.7)	5 (17.2)
ALT increased	0.0	3 (10.0)	4 (13.8)
Hyperhidrosis	0.0	1 (3.3)	4 (13.8)
Muscle spasms	1 (3.2)	2 (6.7)	3 (10.3)
AST increased	0.0	2 (6.7)	3 (10.3)
Alopecia	0.0	3 (10.0)	0.0
Nasopharyngitis	1 (3.2)	2 (6.7)	0.0

One subject from the linsitinib 150 mg BID arm was mis-randomized to placebo and has been included as part of the placebo group for all safety assessments.
AE, adverse event; ALT, alanine transaminase; AST, aspartate transaminase; BID, twice daily; PBO, placebo; TEAE, treatment-emergent adverse event.
Sling Therapeutics. Data on File.

Very Few Treatment-Emergent AEs of Interest Observed

TEAE of Interest	PBO n=31 n (%)	Linsitinib 75 mg BID n=30 n (%)	Linsitinib 150 mg BID n=29 n (%)
Tinnitus	1 (3.2)	1 (3.3)	1 (3.4)
Hypoacusis / hearing impairment	0.0	0.0	1 (3.4)[a]
Glycosylated hemoglobin increased	1 (3.2)	0.0	0.0
Hyperglycemia	0.0	1 (3.3)	1 (3.4)
Menstrual changes	0.0	0.0	0.0

- Minimal and not clinically meaningful AEs relating to hearing, no study drug discontinuations due to hearing AEs
  - 0% placebo adjusted tinnitus rate
  - Only 1 hearing impairment on linsitinib, assessed as unrelated to treatment
- 3.4% (1 out of 29) with hyperglycemia with no medical intervention required to treat
- No observed menstrual changes
- Rigorous assessment by ECG throughout study showed no QTc prolongation in any patient
- No patients TED disease progressed while on treatment

[a]Assessed as unrelated to treatment.
One subject from the linsitinib 150 mg BID arm was mis-randomized to placebo and has been included as part of the placebo group for all safety assessments.
AE, adverse event; BID, twice daily; ECG, electrocardiogram; PBO, placebo; QTc, corrected QT interval.
Sling Therapeutics. Data on File.

As the Only Oral Treatment with a Positive Study in Patients with TED, Linsitinib is Poised to Change the Treatment Paradigm

Given disease biology expect IGF-1R inhibitors to continue to be used first line

There are obstacles associated with existing IGF-1R inhibitors…

- Concern over side effects, particularly hearing impairment and hyperglycemia
- Access to prescribing physicians
- Inconvenience of IV infusions

…which could be overcome with a safe, effective, oral IGF-1R therapy:

- Lower patient hurdles to accepting treatment
- Simplified administration for physicians and patients
- Potential expansion of prescriber base

Rapid response and no disease progression observed on therapy

Minimal downside to initiating linsitinib

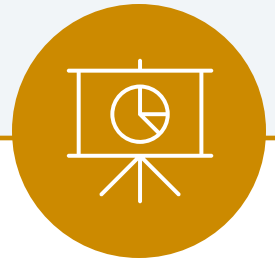
Opportunity for more patients to consider and receive a therapeutic intervention for TED

IGF-1R, insulin-like growth factor 1 receptor; TED, thyroid eye disease.

We are Excited to Continue to Advance Linsitinib as a Treatment Option for Patients with TED

Engage with health authorities to confirm submission requirements

Initiate confirmatory Phase 3 study



Present full results of clinical trial at an upcoming medical meeting

Continue to build and grow our team and program

TED, thyroid eye disease.

Thank you