TONIX PHARMACEUTICALS

TNX-1500

(humanized Fc-modified α-CD40L mAb[1])

Organ Transplant Rejection & Autoimmune Disorders

NASDAQ: TNXP

July 25, 2025

[1]TNX-1500 is an investigational new biologic and is not approved for any indication

P06094 July 26, 2025 (Doc 1611)

Cautionary Note on Forward-Looking Statements

Certain statements in this presentation regarding strategic plans, expectations and objectives for future operations or results are “forward-looking statements” as defined by the Private Securities Litigation Reform Act of 1995. These statements may be identified by the use of forward-looking words such as “anticipate,” “believe,” “forecast,” “estimate” and “intend,” among others. These forward-looking statements are based on Tonix’s current expectations and actual results could differ materially. There are a number of factors that could cause actual events to differ materially from those indicated by such forward-looking statements. These factors include, but are not limited to, the risks related to failure to obtain FDA clearances or approvals and noncompliance with FDA regulations; risks related to the failure to successfully market any of our products; risks related to the timing and progress of clinical development of our product candidates; our need for additional financing; uncertainties of patent protection and litigation; uncertainties of government or third party payor reimbursement; limited research and development efforts and dependence upon third parties; and substantial competition. As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products. The forward-looking statements in this presentation are made as of the date of this presentation, even if subsequently made available by Tonix on its website or otherwise. Tonix does not undertake an obligation to update or revise any forward-looking statement, except as required by law. Investors should read the risk factors set forth in the Annual Report on Form 10-K for the year ended December 31, 2024, as filed with the Securities and Exchange Commission (the “SEC”) on March 18, 2025, and periodic reports and current reports filed with the SEC on or after the date thereof. All of Tonix's forward-looking statements are expressly qualified by all such risk factors and other cautionary statements.

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TNX-1500*

Next Generation

α-CD40 Ligand (CD40L) Antibody

The CD40-CD40L pathway is a pivotal immune system modulator and a well-established and promising treatment target

Differentiators: Expected to deliver efficacy without compromising safety

First Generation: Development halted due to thromboembolic (TE) complications—blood clots—traced to Fc gamma receptor (Fc**γ**R)

Second Generation: Eliminated the Fc**γ**R TE complication but potency and half life was reduced, limiting utility

Third Generation (TNX-1500): Re-engineered to better modulate the binding of Fc**γ**R.

*TNX-1500 has not been approved for any indication. Patents filed.

Prevention of Allograft and Bone Marrow Transplant Rejection

Status: Phase 1 study – completed

Collaborations ongoing with Mass General Hospital on heart and kidney transplantation in non-human primates

- Collaboration with Boston Children's on bone marrow transplantation in non-human primates

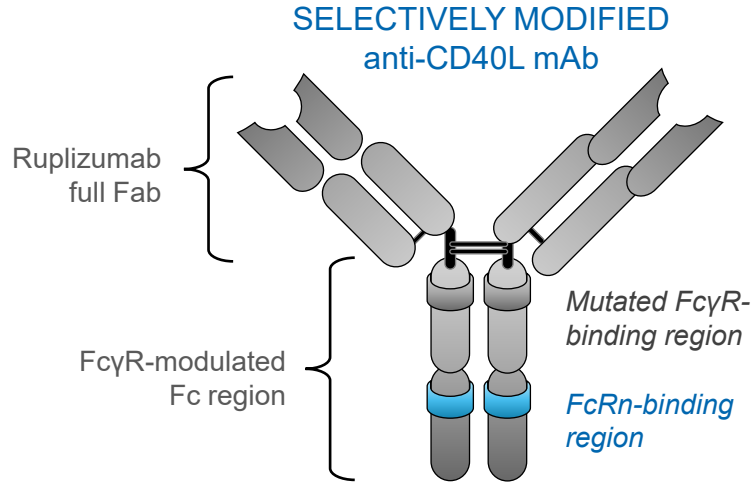
Next Steps: Initiate Phase 2 study in Kidney Transplant Recipients

Autoimmune Diseases

Status: Potential future indications include:

Sjögren's Syndrome, Systemic Lupus Erythematosus

- These indications require large studies, but represent large target markets



Contains the full ruplizumab Fab and the engineered Fc region that modulates FcγR-binding, while preserving FcRn function.

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About CD40L (Also Called CD154)

- **CD40L is a transiently expressed T cell surface molecule and is also called CD154[1-4]**
  - Predominantly expressed by T cells and interacts with CD40 on B cells and macrophages
- **Mediates T cell helper function[1-4]**
  - Activates B cells for humoral (antibody-mediated) immune response
  - Activates macrophages and dendritic cells
  - Provides T cell help to activated CD8+ T cells
- **X-linked hyper-IgM syndrome is caused by a defective CD40L gene[5-6]**
  - Lack of T helper function with only IgM serum antibodies but no IgG or IgE because T cells are required for B cell isotype switching
  - If maintained on gamma globulin, patients are otherwise healthy
- **Member of the TNFα superfamily[4]**
  - TNFα, RANKL, TL1a and CD30L are other family members and are drug targets
    - α-TNFα, and α-RANKL approved (*e.g.*, Humira® and Prolia®)

[1]Lederman S, et al. *J Exp Med*. 1992;175(4):1091-1101.
[2]Lederman S, et al. *J Immunol*. 1992;149(12):3817-3826.
[3]Lederman S, et al. *J Immunol*. 1994;152(5):2163-2171.
[4]Covey LR, et al. *Mol Immunol*. 1994;31(6):471-484
[5]Ramesh N, et al. *Int Immunol*. 1993;5(7):769-773.
[6]Callard RE, et al. *J Immunol*. 1994;153(7):3295-3306.

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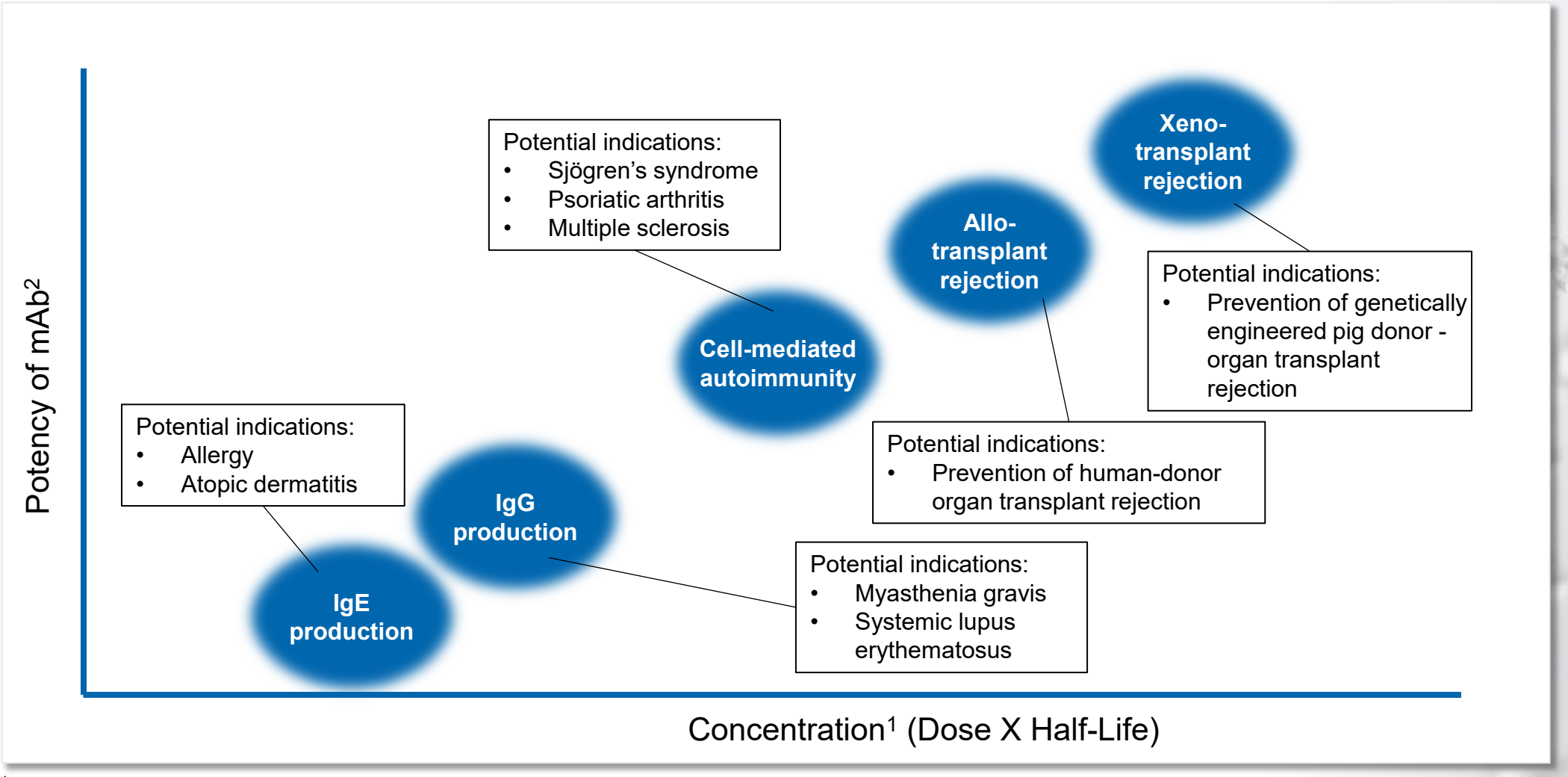
α-CD40L Effects on Humoral and Cellular Immunity in Animal Models is Dependent on Potency and Concentration

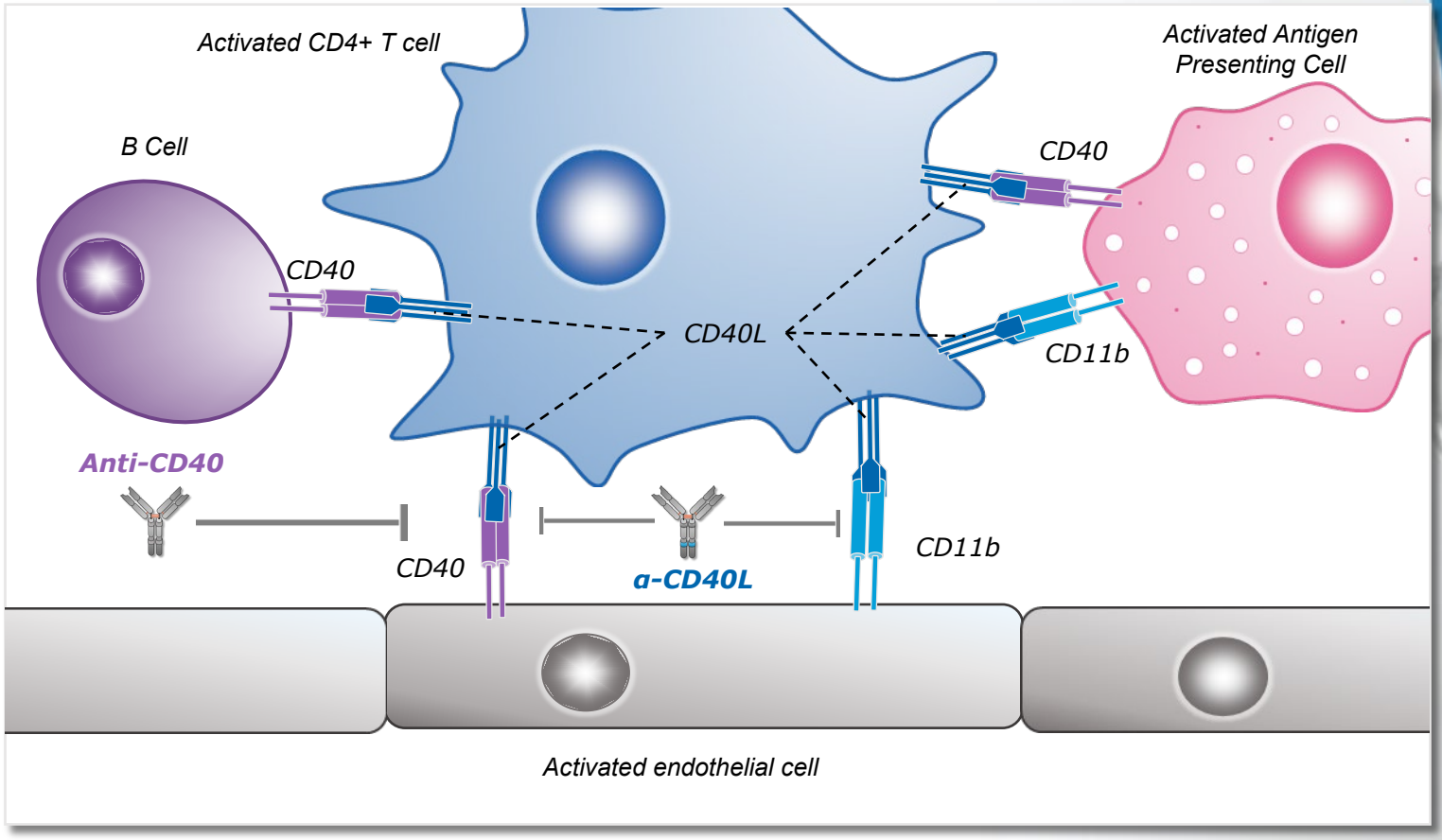


[1]Concentration is dependent on dose and half-life
[2]Potency depends on binding affinity and other factors, *e.g.* neutralization of CD40L trimers

IgE=immunoglobulin E; IgG=immunoglobulin G; mAb=monoclonal antibody.

CD40L is a Ligand for Both CD40 and CD11b

- Blocking interaction of CD40L and CD11b enhances efficacy of anti-CD40 treatment in prolonging allograft survival[1]
  - α-CD40 antibodies block CD40/CD40L binding, but do not affect CD11b/CD40L binding[1]
- α-CD40L antibodies may offer the advantage of blocking interaction with both CD40 and CD11b

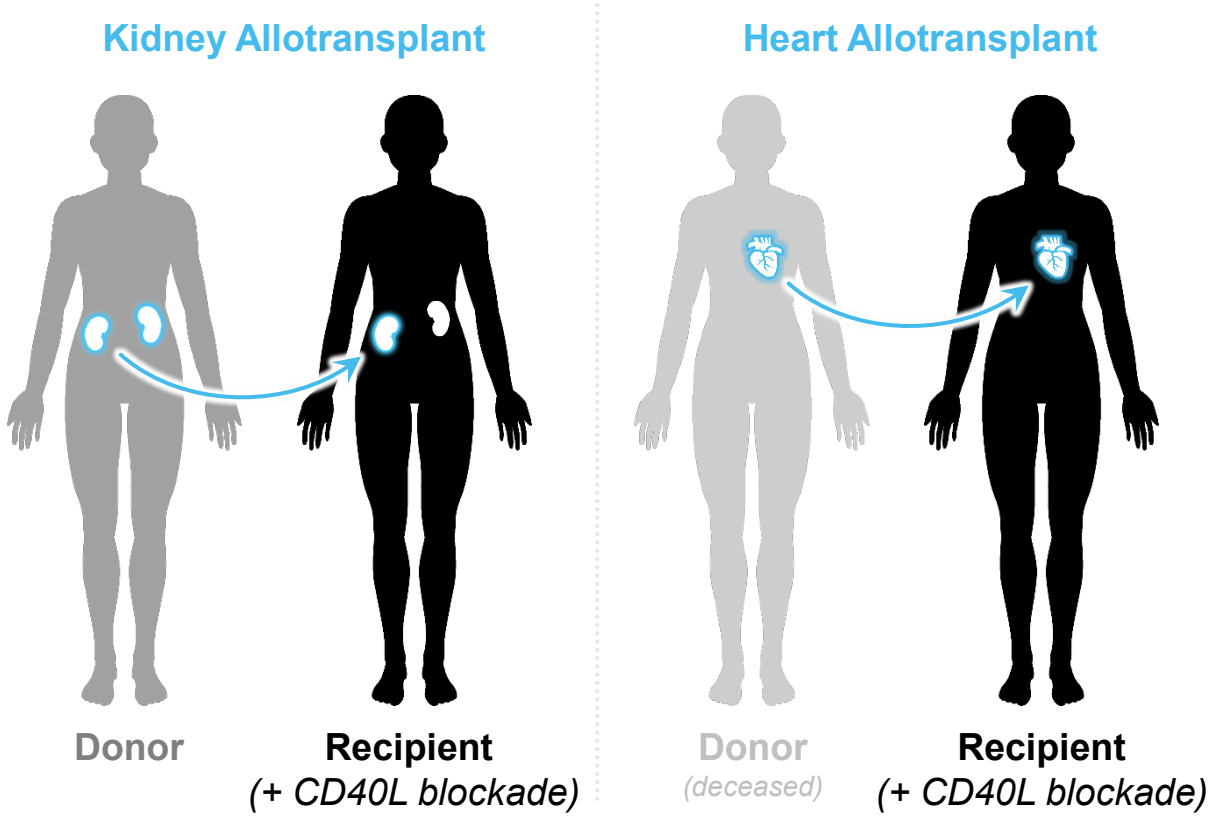


[1]Liu D, et al. *Am J Transplant*. 2020;202216-2225.

α-CD40L Treatment to Prevent Allograft Rejection

- Calcineurin inhibitors (CNIs), mainly tacrolimus, are the cornerstone of immunosuppressive therapy[1,2]
- However, CNIs cause irreversible and progressive deterioration of kidney function in all types of solid organ transplants[3,4]
- Costimulation blockade (α-CD40L in particular) may be more effective at protecting allografts than CNIs[5]

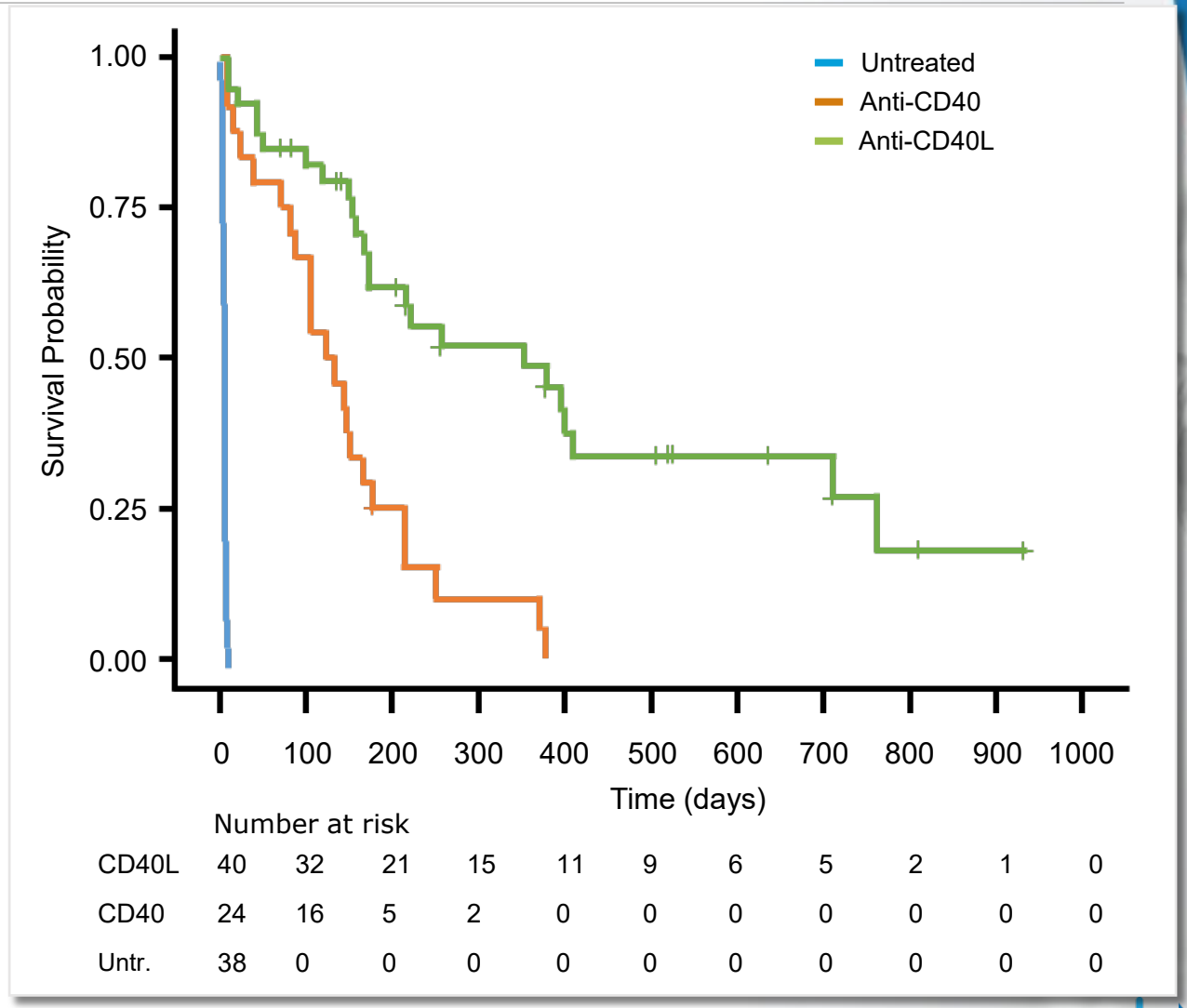
Concept for Human-to-Human Allotransplantation[1,2]



[1]Enderby C, et al. *Am J Manag Care*. 2015;21(1 Suppl):s12-s23.
[2]Camilleri B, et al. *Exp Clin Transplant*. 2016;14(5):471-483.
[3]Naesens M, et al. *Clin J Am Soc Nephrol*. 2009;4(2):481-508.
[4]Nankivell BJ, et al. *N Engl J Med*. 2003;349(24):2326-2333.
[5]Cooper DKC, et al. *Blood Purif*. 2018;45(1-3):254-259.

CD40L Inhibition Offers Decreased Risk of Graft Rejection and Increased Survival vs CD40 Inhibition[1]

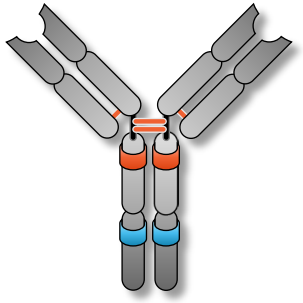
- A meta-analysis of nonhuman primate studies compared α-CD40 and α-CD40L treatments for the prevention of renal transplant rejection
  - Both treatments increased probability of rejection-free survival compared to placebo
  - α-CD40L treatment resulted in a median survival of 352 days vs 131 days for α-CD40 treatment (P=0.0001)



[1]Perrin S, et al. *Front Immunol.* 2022;13:861471.

Third-Generation α-CD40L Engineered to Decrease Risk of Thrombosis

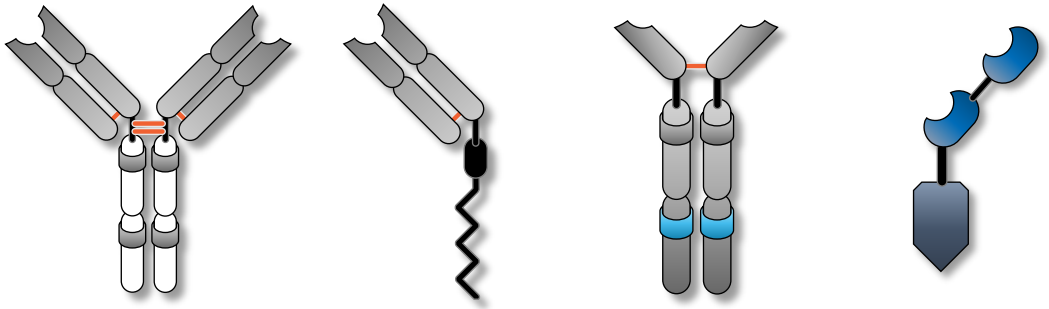
First-generation anti-CD40L mAbs



Ruplizumab

Constant fragment (Fc) domain interacted with FcγRIIA (CD32A), which suggested a mechanism for the increased risk of thrombosis.[1,2]

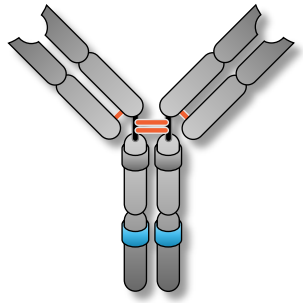
Second-generation anti-CD40L proteins



Aglycosyl Ruplizumab | *Dapirolizumab* | *Letolizumab* | *Dazodalibep*

Second-generation anti-CD40L proteins exhibited dramatically reduced binding to FcγRIIA[3-6] but had other issues, including decreased efficacy, shortened half-life, or engendering of anti-drug antibodies (ADAs).[7-9]

Third-generation anti-CD40L mAbs*



TNX-1500

TNX-1500 is engineered to target CD40L therapeutically while reducing FcγRIIA binding and thereby lowering the potential for thrombosis.[1-9]

***Sanofi's frexalimab (formerly SAR441344) and Eledon's tegoprubart (formerly AT-1501) also are Fc-modified third-generation anti-CD40L mAbs**

[1]Inwald DP, et al. *Circ Res*. 2003;92(9):1041-1048.
[2]Robles-Carrillo L, et al. *J Immunol*. 2010;185(3):1577-1583.
[3]Shock A, et al. *Arthritis Res Ther*. 2015;17(1):234.
[4]Xie JH, et al. *J Immunol*. 2014;192(9):4083-4092.
[5]Ferrant JL, et al. *Int Immunol*. 2004;16(11):1583-1594.
[6]Karnell JL, et al. *Sci Transl Med*. 2019;11(489):eaar6584.
[7]ClinicalTrials.gov identifier: NCT02273960. Updated July 16, 2019. Accessed June 1, 2021. https://clinicaltrials.gov/ct2/show/results/NCT02273960?view=results
[8]Waters J, *Biocentury*; October 26, (2018).
[9]Company data.

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TNX-1500 Preclinical Data and Publications

Non-human Primate Kidney Allo-Transplantation

- TNX-1500 monotherapy consistently prevents kidney transplant rejection with no thrombosis observed
- April 2023 Publication: Lassiter, G., et al. (2023). TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Renal Allograft Survival. *American Journal of Transplantation*. www.sciencedirect.com/science/article/pii/S1600613523003714

Non-human Primate Heart Heterotopic Allo-Transplantation

TNX-1500 monotherapy consistently prevents heart transplant rejection. Similar activity to chimeric hu5c8 during treatment phase in prior studies

April 2023 Publication: Miura, S., et al. (2023) TNX-1500, an Fc-modified Anti-CD154 Antibody, Prolongs Nonhuman Primate Cardiac Allograft Survival. *American Journal of Transplantation.* www.sciencedirect.com/science/article/pii/S1600613523003969

Non-Human Primate Kidney Xenograft Transplantation

TNX-1500 therapy is part of a regiment to prevent rejection in kidney xenograft transplants

- Anand, R.P., Layer, J.V., Heja, D. et al. (2023). Design and testing of a humanized porcine donor for xenotransplantation. *Nature.* https://www.nature.com/articles/s41586-023-06594-4
- Kozlov, M. (2023). Monkey survives two years after gene-edited pig-kidney transplant. *Nature.* https://www.nature.com/articles/d41586-023-03176-2
- Mohiuddin, M. (2023). Pig-to-primate organ transplants require genetic modifications of donor. *Nature.* https://www.nature.com/articles/d41586-023-02817-w

TNX-1500 (α-CD40L) for Preventing Rejection in Organ Transplant
Six-month (+) data

Two papers published in the August 2023 edition of the *American Journal of Transplantation*[1,2]

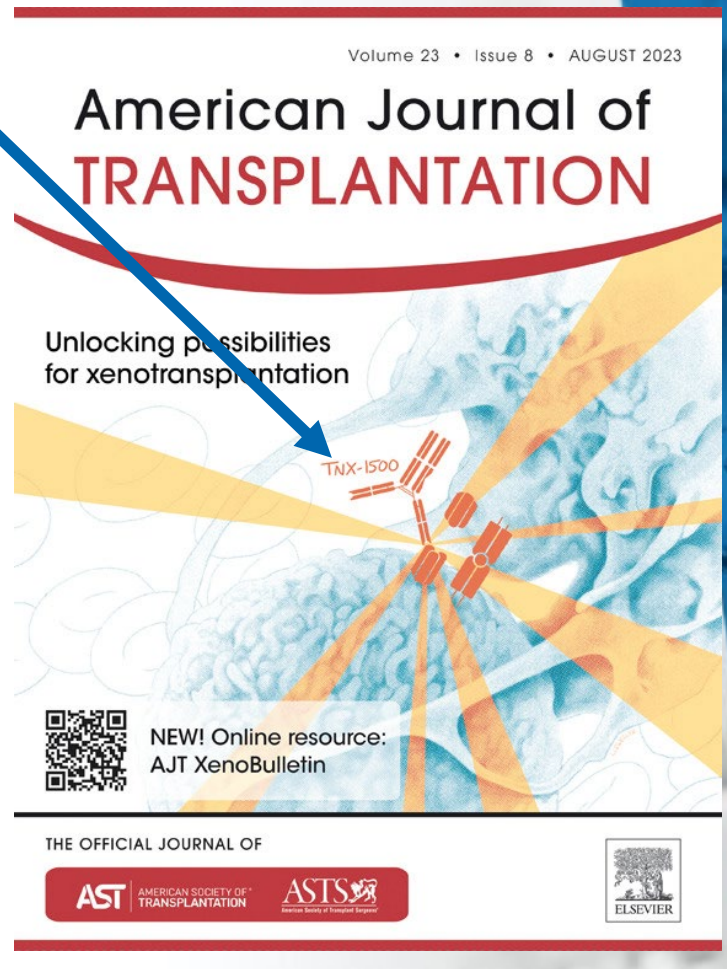
- No apparent loss of effector function with Fc-modified TNX-1500 mAb relative to hu5c8

Allo-kidney transplants in animals[1]

- TNX-1500 monotherapy consistently prevents kidney transplant rejection
- Superior to results with conventional triple drug immunosuppressive regimen[3]
- No thrombosis observed
- Includes data suggesting that mycophenolate (MMF) may inhibit the ability of anti-CD40L to prevent rejection and may lower the number of T-regulatory cells (T_{reg}'s)

Allo-heart transplants in animals[2]

- TNX-1500 monotherapy consistently prevents heart transplant rejection
- Prolonged acceptance after cessation of therapy (in progress)
- Similar activity to chimeric hu5c8 during treatment phase in prior studies
- Reported a statistically significant change in the ratio of T-effector (T_{eff}) and T_{reg} cells (T_{eff}/T_{reg}) with "standard" dose TNX-1500 relative to low dose TNX-1500, or to low dose TNX-1500 plus MMF



[1]Lassiter G, et al. *Am J Transplant*. 2023. 23(8):1171-1181. doi: 10.1016/j.ajt.2023.03.022
[2]Miura S, et al. *Am J Transplant.* 2023. 23(8):1182-1193. doi: 10.1016/j.ajt.2023.03.025
[3]Tacrolimus, MMF and steroids

Non-Human Primate Kidney Xenograft Transplantation
Dr. Tatsuo Kawai, Mass General Hospital

- **TNX-1500 therapy is part of a regiment to prevent rejection in kidney xenograft transplants**
  - Prolonged acceptance

- **October 11, 2023 - Publication and news coverage in *Nature***
  - Anand, R.P., Layer, J.V., Heja, D. *et al.* Design and testing of a humanized porcine donor for xenotransplantation. *Nature* 622, 393–401 (2023). https://doi.org/10.1038/s41586-023-06594-4. URL: Design and testing of a humanized porcine donor for xenotransplantation | Nature[1]
  - Kozlov, M. Oct 11, 2023 News: “Monkey survives two years after gene-edited pig-kidney transplant” *Nature* URL: Monkey survives for two years after gene-edited pig kidney transplant (nature.com)
  - Mohiuddin, M. Oct 11, 2023 *Nature*. News and Views. “Pig-to-primate organ transplants require genetic modifications of donor.” URL: Pig-to-primate organ transplants require genetic modifications of donor (nature.com)

[1]In Arnand et al., Table 1, I see four TNX-1500 treated animals: M8220, M6421, M12621, M5722

Non-Human Primate Bone Marrow Transplantation
Dr. Leslie Kean[1], Boston Children's Hospital/Dana Farber

Studying TNX-1500 in combination with other drugs for preventing rejection and graft versus host disease (GvHD) in bone marrow transplant[2]

- Hematopoietic Stem Cell Transplantation (HCT) from unrelated donors is a component of the treatment protocol for several hematologic malignancies
- GvHD complicates treatment and limits the success of engraftment after HCT
- To be successful, the post-HCT indication requires prolonged engraftment.
- GvHD remains one of the most severe complications associated with HCT. For myeloablative MHC-haploidentical HCT, the risk of GvHD is substantial, and with the most severe form of acute GvHD, as many as half of patients can die from this disease. For these high-risk transplants, there is no fully effective GvHD prevention strategy.
- The primary objective of the preclinical research study is to study the activity of TNX-1500 administered prophylactically to modify GvHD progression in animals after HCT to support an Investigational New Drug (IND) application for human studies

Prof. Kean is a leader in the field of NHP bone marrow transplants

- Unique model of haplo-identical animals[3]

[1]The principal investigator is Leslie S. Kean M.D., Ph.D., Director, Stem Cell Transplantation Program, Division of Hematology/Oncology, Boston Children's Hospital, Department of Pediatric Oncology, Dana-Farber Cancer Institute and Robert A. Stranahan Professor of Pediatrics, Harvard Medical School.
[2]Tonix Press Release. Dec 5, 2022. https://ir.tonixpharma.com/news-events/press-releases/detail/1353/tonix-pharmaceuticals-announces-collaboration-with-boston
[3]Tkachev V, et al. 2017. *Sci Transl Med*.9(408):eaan3085. doi: 10.1126/scitranslmed.aan3085. PMID: 28931653; PMCID: PMC5681253.

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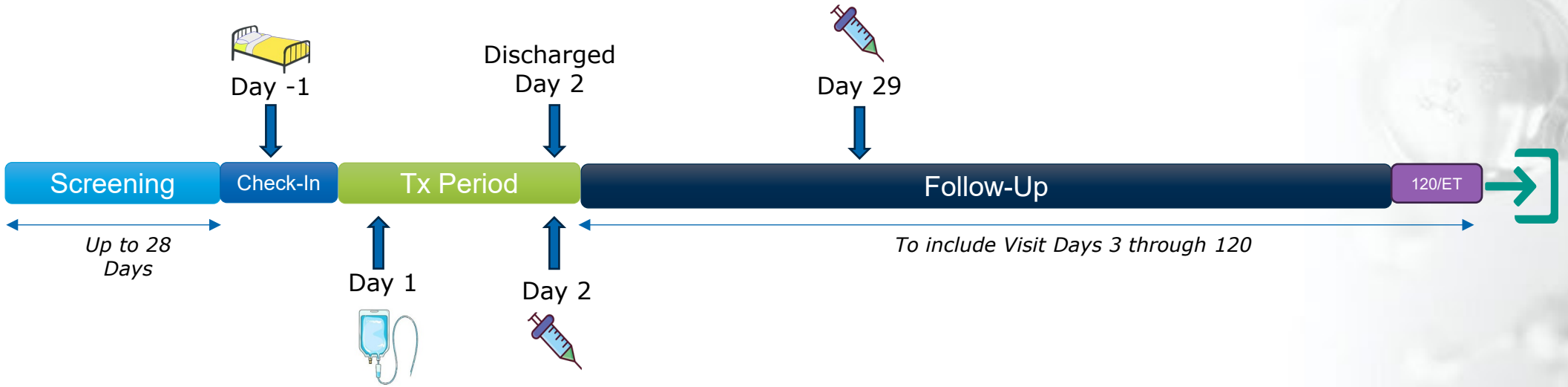
TNX-1500 Phase 1 Study Design (1 of 2)



Legend:

- Check-in Day at CRC
- TNX-1500/Placebo Administration
- KLH Administration, observed for 1 hour post dose
- Exit Study

IMMUNOLOGY PORTFOLIO

TNX-1500: Phase 1 Study Design (2 of 2)

Cohort	Number of Subjects	Dose Level (IV)
Cohort 1	6 (4 active, 2 placebo)	3 mg/kg
Cohort 2	10 (8 active, 2 placebo)	10 mg/kg
Cohort 3	10 (8 active, 2 placebo)	30 mg/kg

TNX-1500 Phase 1 Results and Methods

Topline Results

- Tolerability: TNX-1500 was generally well-tolerated with a favorable safety and tolerability profile. The only TEAE occurring in ≥ 3 participants among all TNX-1500 groups was Aphthous ulcer, occurring in one participant each in the 3 mg/kg, 10 mg/kg, and 30 mg/kg groups; all were rated as mild, possibly related, and resolved in 2-10 days. There were no TEAEs assessed as related to KLH administration. No TEAEs led to study discontinuation. There were no serious adverse events. There were no thromboembolic events, which were prespecified as TEAEs of special interest.
- Pharmacodynamics: TNX-1500 at 10 mg/kg and 30 mg/kg blocked both the primary and secondary anti-KLH Ab responses, evidenced by the mean Ab level at all sampled timepoints (through Day 120) being below the lower limit of quantitation (400 µg/L). TNX-1500 at 3 mg/kg blocked the primary response to KLH Day 2 challenge and reduced the peak secondary response to KLH Day 29 challenge by approximately two thirds (69%) relative to the peak response to placebo.
- Pharmacokinetics: The mean (SD) half-life ($t_{1/2}$) of TNX-1500 was: 3 mg/kg, 19.6 (9.29) days; 10 mg/kg, 37.8 (5.46) days; and 30 mg/kg, 33.7 (4.83) days.

Methods

- Dosing: TNX-1500 solution for IV infusion was infused over a period of one hour to achieve doses of 3, 10, and 30 mg/kg. Participants were observed in the clinic for one day and followed with periodic clinic visits to Day 120.
- Keyhole Limpet Hemocyanin (KLH) Challenge: To evaluate the immune modulation potency of TNX-1500, participants received an antigen challenge with KLH (Immucothel®) administered subcutaneously (SC) on Day 2 and Day 29 of the study. Samples for anti-KLH antibody (Ab) were obtained on Days 1 (pre-challenge), 8, 15, 29, 36, 50, 64, 78, and 120.
- Disposition: At total of 26 participants were enrolled in three Cohorts (Cohort 1: n=4 at 3 mg/kg, n=2 placebo; Cohort 3: n=8 at 10 mg/kg, n=2 placebo; Cohort 3: n=8 at 30 mg/kg, n=2 placebo). A total of 24 participants completed the study and two discontinued early (one placebo participant was lost to follow-up and one on TNX-1500 withdrew consent).

TNX-1500 Phase 1 Topline Results and Conclusions

Phase 1 design – single ascending dose study in healthy participants

- Goals: Evaluate safety, pharmacodynamics and pharmacokinetics
- At total of 26 participants were enrolled in three cohorts
  - 3 mg/kg, 10 mg/kg, and 30 mg/kg

Topline results

- Pharmacodynamics: TNX-1500 blocked the primary and secondary antibody responses to a test antigen (KLH) at the 10 and 30 mg/kg IV doses
- Pharmacokinetics: mean half-life ($t_{1/2}$) for the 10 mg/kg and 30 mg/kg doses of 34-38 days
- TNX-1500 was generally well-tolerated with a favorable safety profile
- Tolerability: TNX-1500 was generally well-tolerated with a favorable safety and tolerability profile. The only TEAE occurring in ≥ 3 participants among all TNX-1500 groups was Aphthous ulcer, occurring in one participant each in the 3 mg/kg, 10 mg/kg, and 30 mg/kg groups; all were rated as mild, possibly related, and resolved in 2-10 days.

Conclusions

- Results support proceeding to develop Phase 2 trial for the prevention of kidney transplant rejection
- Fc modifications we engineered to TNX-1500 for safety did not attenuate the potency of TNX-1500 relative to humanized 5c8 (hu5c8, ruplizumab, BG9588)[1-3]
- We believe the results of this study and our prior animal studies[4,5] indicate that TNX-1500 is potentially best-in-class among anti-CD40L mAbs in development

1. Lederman S, et al, *J Exp Med*. 1992 Apr 1;175(4):1091-101. doi: 10.1084/jem.175.4.1091. PMID: 1348081; PMCID: PMC2119166.
2. Boumpas DT, et. al. *Arthritis Rheum*. 2003;48(3):719-27. doi: 10.1002/art.10856. PMID: 12632425.
3. Pierson RN 3rd, et al. *Transplantation*. 1999;68(11):1800-5. doi: 10.1097/00007890-199912150-00026. PMID: 10609959.
4. Lassiter G, et al. *Am J Transplant*. 2023;23(8):1171-1181. doi: 10.1016/j.ajt.2023.03.022.
5. Miura S, et al. *Am J Transplant*. 2023;23(8):1182-1193. doi: 10.1016/j.ajt.2023.03.025.

Other α-CD40L Monoclonal Antibodies in Development

Sanofi – Frexalimab, Indications: Multiple Sclerosis (MS), Systemic Lupus Erythematosus (SLE)

- Sjögren's Syndrome (SjS) (NCT04572841) program discontinued[1]
- Phase 2 Trial in Relapsing MS reported in the *NEJM* (NCT04879628)[2]
- Phase 2 Trial planned in SLE (NCT05039840)
- Frexalimab, f.k.a.SAR441344 (Fc-modified)

Eledon – Tegoprubart, Indication: Kidney Transplant

- Phase 2 Trial Completed in ALS (NCT04322149)
- Phase 1/2 Trial completed enrollment in Kidney Transplant (NCT05027906)
- Tegoprubart, f.k.a. AT-1501 (Fc-modified)

Biogen/UCB – Dapirolizumab pegol, Indication: Systemic Lupus Erythematosus (SLE)

- Phase 3 Trial (NCT04294667) reported positive topline results[3]
- Dapirolizumab pegol (pegylated Fab)

Amgen (acquired Horizon) – Dazodalibep, Indication: Sjögren's Syndrome (SjS)

- Two cohorts with statistically significant results in a Phase 2 study reported[4,5]
- Dazodalibep (tn03 fusion protein)

Lundbeck and AprilBio – Lu AG22515, Indication: Neurology

- Phase 1 Trial in Healthy Adults complete (NCT05136053)
- APB-A1 or Lu AG22515 (HAS fusion protein)

[1]Tong, A. April 25, 2024. Endpoints. "Sanofi spotlights early-stage cancer assets, counts on grandfather clause on Biosecure"
[2]Vermersch P, et al. N Engl J Med. 2024 Feb 15;390(7):589-600. doi: 10.1056/NEJMoa2309439. PMID: 38354138

[3] Gelman, M. Endpoints. "Biogen, UCB detail response rates in Phase 3 lupus trial after surprising Success" Nov. 19, 2024
[4]https://www.biospace.com/article/releases/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-dazodalibep-for-the-treatment-of-sjoegren-s-syndrome-meets-primary-endpoint/
[5]https://www.businesswire.com/news/home/20230118005359/en/Horizon-Therapeutics-plc-Announces-Phase-2-Trial-Evaluating-Dazodalibep-for-the-Treatment-of-Sj%C3%B6gren%E2%80%99s-Syndrome-Meets-Primary-Endpoint-in-the-Second-Study-Population-

α-CD40L Headlines

- Mass General Hospital has transplanted genetically engineered pig kidneys into living humans[1]
  - *e.g.*, Boston Globe, March 21, 2024
  - Patient's death announced May 11, 2024[2]
- The patient is being treated with anti-CD40L mAb tegoprubart from Eledon[1]
- ***The preclinical work was performed with TNX-1500***[3]
- Mass General wants to perform allo kidney transplants with TNX-1500 under investigator-initiated IND

The Boston Globe

In a first, Mass. General surgeons transplant a pig kidney into a man

The patient is doing well, but many unknowns remain

By Felice J. Freyer Globe Staff, Updated March 21, 2024, 7:40 p.m.

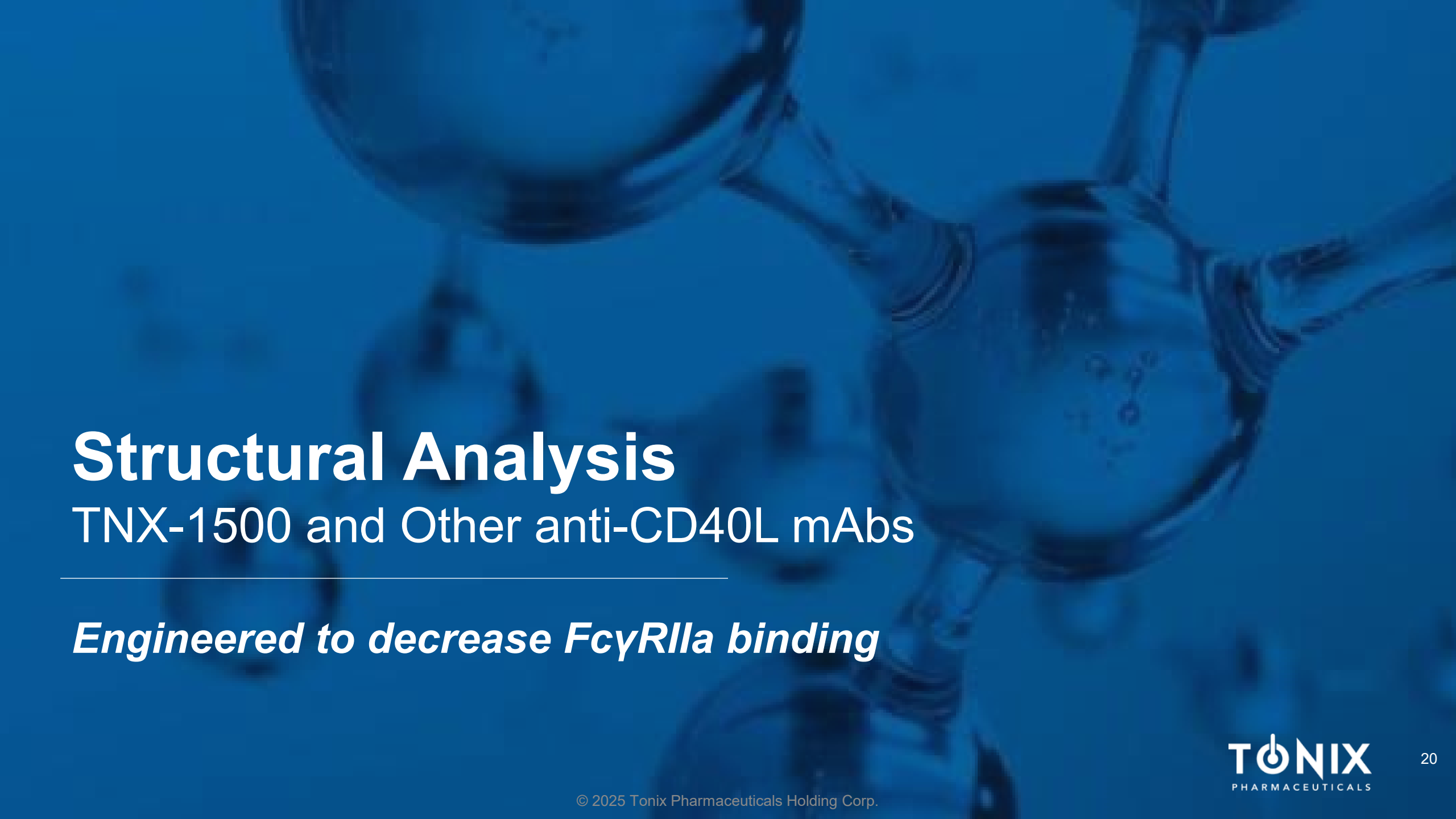
Dr. Leonardo V. Riella, medical director of kidney transplantation, center, broke down as he thanked his colleagues. Dr. Tatsuo Kawai, director of the Legorreta Center for Clinical Transplant Tolerance, left, and Dr. Winfred Williams, associate chief of the Division of Nephrology, also spoke at a news conference on Thursday. DAVID L. RYAN/GLOBE STAFF

Seventy years after surgeons at Brigham & Women's Hospital performed the world's first kidney transplant, doctors at its sister hospital, Massachusetts General, announced an

[1] Massachusetts General Hospital press release. March 21, 2024. "World's First Genetically Edited Pig Kidney Transplant into Living Recipient Performed at Massachusetts General Hospital." www.massgeneral.org/news/press-release/worlds-first-genetically-edited-pig-kidney-transplant-into-living-recipient (accessed March 29, 2024)

[2] Stoico, N. *Boston Globe*. May 11, 2023. "Mass Man who received first kidney transplant from genetically engineered pig has died, family says".

[3] Anand, R.P., et al *Nature*. 622, 393–401 (2023). https://doi.org/10.1038/s41586-023-06594-4

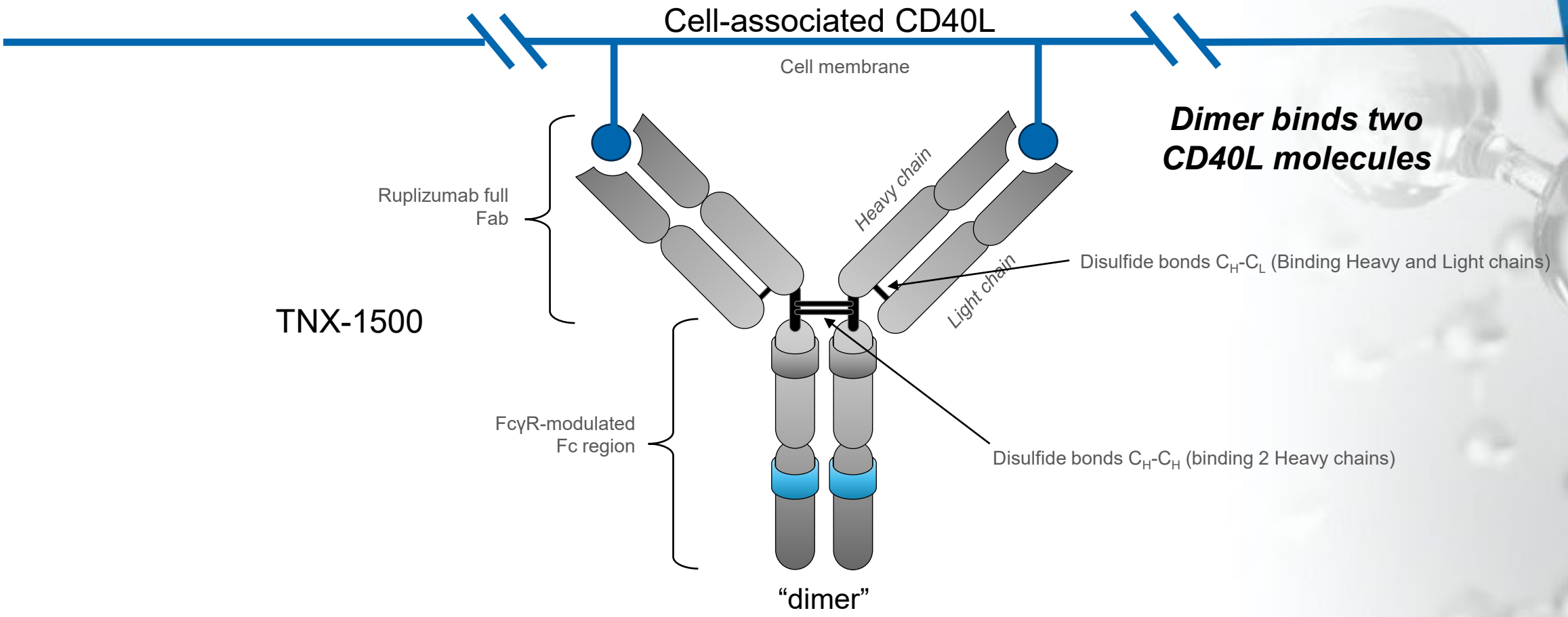


Structural Analysis

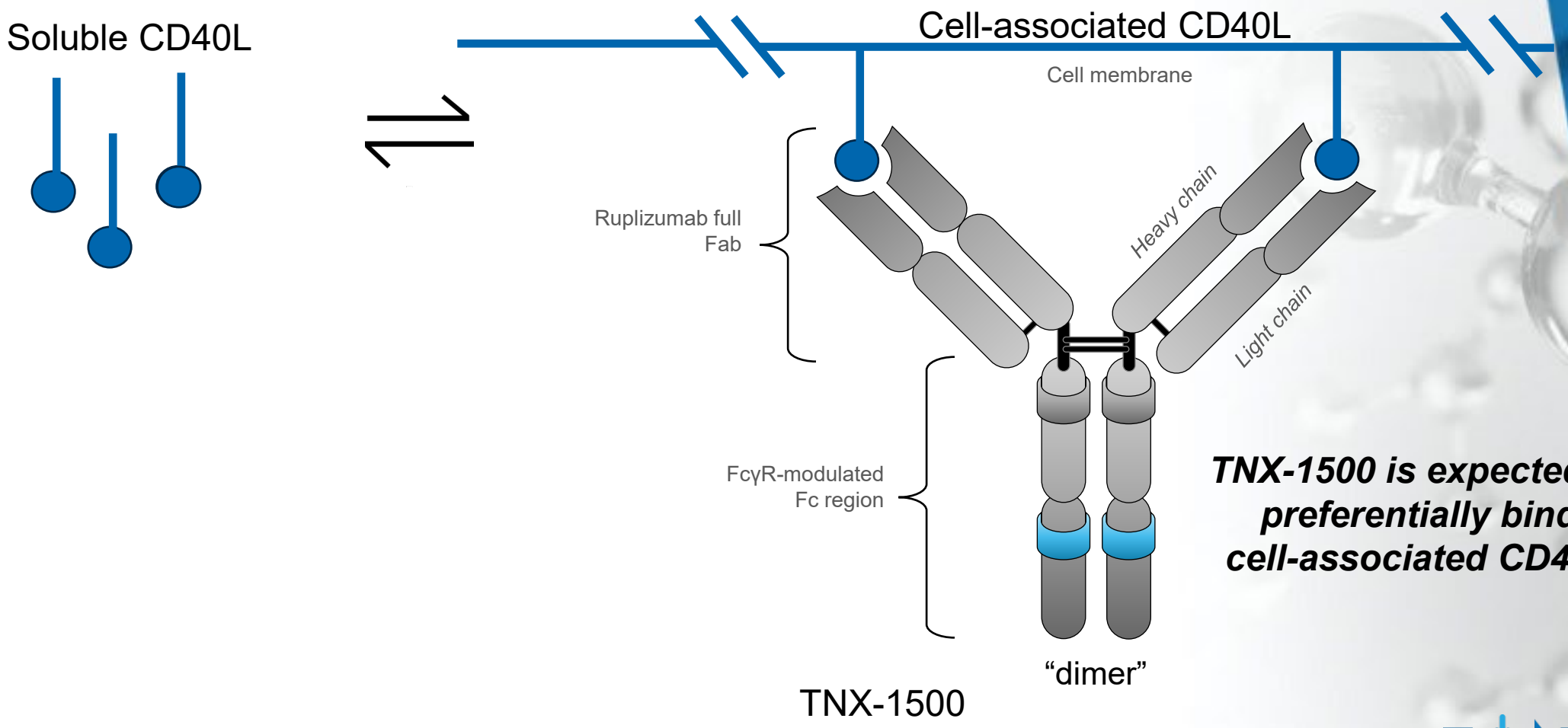
TNX-1500 and Other anti-CD40L mAbs

Engineered to decrease FcγRIIa binding

TNX-1500 (α-CD40L) for Organ Transplant



CD40L has Soluble and Cell-Associated Forms



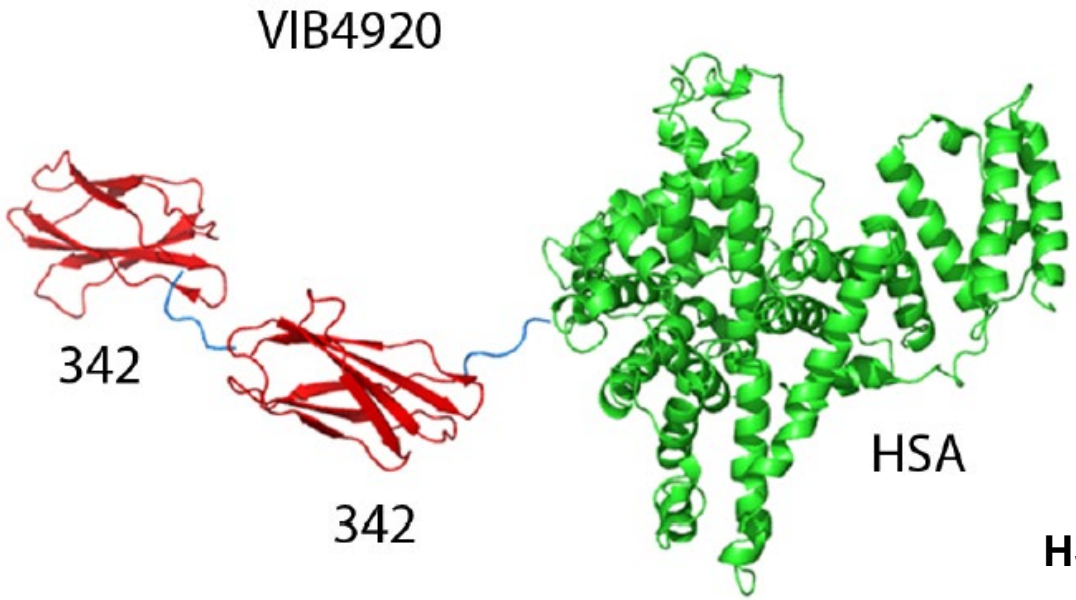
TNX-1500 is expected to preferentially bind cell-associated CD40L

IMMUNOLOGY PORTFOLIO

TONIX PHARMACEUTICALS

Amgen/Horizon's Dazodalibep α-CD40L is an Albumin Fusion Protein

- Amgen's (formerly Horizon's) Dazodalibep (tn03 fusion protein)
  - Is an albumin fusion protein with no Ig Fc region – Figure reproduced from Karnell et al.[1]
  - Formerly known as VIB4920
  - Reported two positive cohorts in a Phase 2 Sjögren's trial



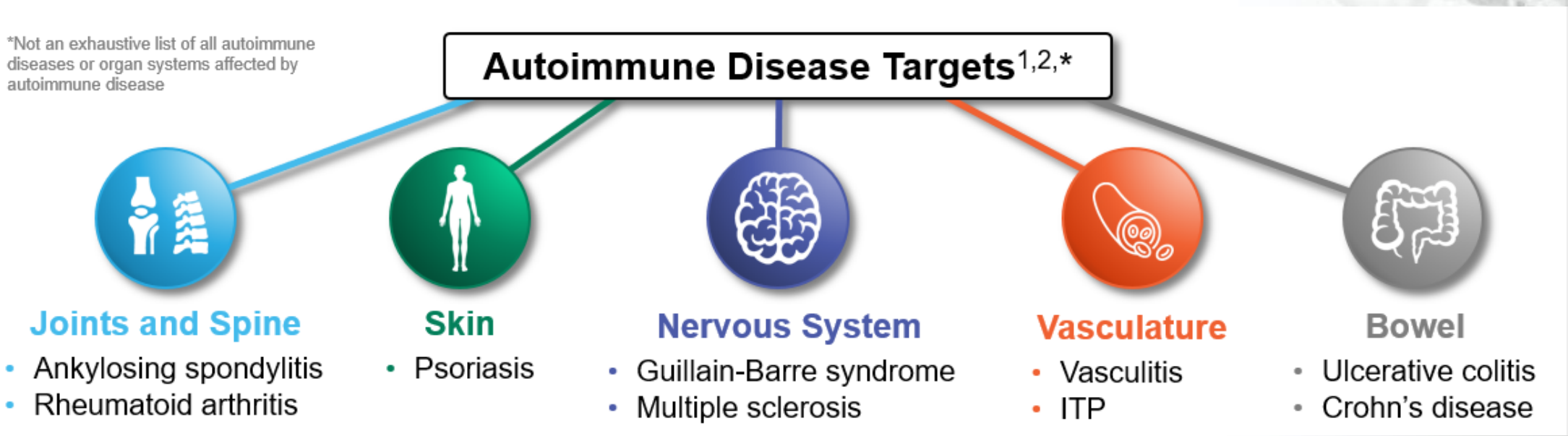
HSA = Human Serum Albumin

[14]Karnell JL, et al. *Sci Transl Med.* 2019. 11(489):eaar6584. doi: 10.1126/scitranslmed.aar6584. PMID: 31019027.

Autoimmune Disease

α-CD40L Beyond Allografts: Autoimmunity

- Autoimmune diseases are also characterized by immune system activity that attacks "self," which can damage various parts of the body[1,2]
- First-generation anti-CD40L Abs showed evidence of efficacy in autoimmunity before trials were halted due to thromboembolic events[3]



[1]Li P, et al. *Front Pharmacol.* 2017;8:460.
[2]WebMD. Accessed March 3, 2020. https://www.webmd.com/a-to-z-guides/autoimmune-diseases
[3]Tocoian A, et al. *Lupus.* 2015;24(10):1045-1056.

TNFα Superfamily Members Are Targeted by mAbs

- CD40L is a member of the Tumor Necrosis Factor (TNFα) Superfamily[1]
- Other TNFα Superfamily members have proven to be effective targets for antagonist (blocking) mAbs[2]

α-TNFα mAbs for the treatment of certain autoimmune conditions

- infliximab (Remicade®)
- adalimumab (Humira®)

TNFα antagonist receptor fusion protein

- etanercept (Enbrel®)

α-RANKL (CD254) mAb for the treatment of osteoporosis, treatment-induced bone loss, metastases to bone, and giant cell tumor of bone

- denosumab (Prolia® or Xgeva®)

No mAb against CD40L has been licensed *anywhere* in the world

[1]Covey, L.R., et al. *Mol. Immunol.* 31:471-484. 1994. PMID: 7514269.
[2]Remicade® and Simponi® are trademarks of Janssen; Humira® is a trademark of AbbVie; Cimzia® is a trademark of UCB; Enbrel® is a trademark of Amgen; and Prolia® and Xgeva® are trademarks of Amgen.

TNX-1500 (α-CD40L mAb): Prophylaxis of Transplant Rejection
Potential Treatment for Autoimmune Conditions

Phase 2-ready Candidate

Targeted as a first-line monotherapy for autoimmunity and add-on therapy for preventing organ transplant rejection

- Distinct mechanism of action (MOA)—TNX-1500 blocks T cell helper function

New molecular entity, biologic

- US Patient Protection and Affordable Care Act provides 12 years of exclusivity for biologics

Patent applications directed to composition of matter

- Expected patent protection through 2039

Significant Unmet Need

Clinical evidence for anti-CD40L mAbs in the treatment of systemic lupus erythematosus (SLE), Sjögren's Syndrome (SjS), multiple sclerosis, allogeneic kidney transplant and bone marrow transplant

- Several studies have shown anti-CD40L to be active in the treatment of human SLE[1-3], SjS[4,5], and transplant rejection[6,7]

[1]Huang W, et al. *Arthritis Rheum*. 2002;46(6):1554-1562.
[2]Boumpas DT, et al. *Arthritis Rheum*. 2003;48(3):719-727.
[3]Grammer AC, et al. *J Clin Invest*. 2003;112(10):1506-1520.
[4]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating
[5]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-0
[6]Kawai T, et al. *Nat Med*. 2000;6(2):114.
[7]Koyama I, et al. *Transplantation*. 2004;77(3):460-462.

TONIX PHARMACEUTICALS

α-CD40L has Effects on Humoral and Cellular Immunity

In animal models, α-CD40L blocks:

- **Very low doses - IgE production**
  - Potential indications: allergy, atopic dermatitis
- **Low doses – IgG production and humoral autoimmunity**
  - Potential indications: Myasthenia Gravis, Systemic Lupus Erythematosus
- **Low/Middle doses – Cell-mediated autoimmunity**
  - Potential indications: Sjogren's Syndrome, Psoriatic Arthritis, Multiple Sclerosis
- **High/Middle doses – Allo-Transplant rejection**
  - Potential indications: Prevention of rejection of human organs
- **High doses – Xeno-Transplant rejection**
  - Potential indications: Prevention of rejection of Genetically Engineered Pig Organs

Note: only potent α-CD40L mAbs are expected to work on allo-transplant

TNX-1500 Strategy and Status (1 of 2)

1 Prevention of Allograft Rejection

Status: ***Clinical stage Phase 1 completed – positive topline reported in 1st Quarter 2025***

Collaborations ongoing with Mass General Hospital on allo-heart and kidney transplantation in non-human primates

Next Steps: Proceed to develop Phase 2 study in Kidney Transplant Recipients

2 Prevention of Xenograft Rejection

Status: Preclinical studies underway

Collaborations ongoing with Mass General Hospital on xeno-heart and kidney transplantation in non-human primates

Next Steps: Proceed to develop Emergency Use/Compassionate Use IND and protocol

3 Prevention of Allograft Rejection in Sensitized Patients

Status: Preclinical date published by Duke on 5c8 (parent antibody)[1]

Next Steps: Pursuing a collaboration with Duke for Phase 2 study

[1]Anwar, IJ et al., Science Trans Med. 2025. 17: 779. DOI: 10.1126/scitranslmed.adn8130

TNX-1500 Strategy and Status (2 of 2)

4

Common Autoimmune Diseases (e.g., Systemic Lupus Erythematosus [SLE], Multiple Sclerosis, Sjögren's Syndrome, Psoriatic Arthritis)

- These indications require large studies, but represent large target markets
- Planning a partnership on preselecting patients for SLE trial using complimentary diagnostic

5

Rare Autoimmune Diseases (e.g., Myasthenia Gravis, Chronic inflammatory demyelinating polyneuropathy [CIDP], Warm autoimmune hemolytic anemia (wAIHA), fetal neonatal alloimmune thrombocytopenia (FNAIT), Hemolytic disease of the fetus and newborn (HDFN)

- These indications require smaller studies, but have potential for "orphan pricing"

6

Allergic Conditions (e.g., Atopic Dermatitis, COPD with IgE)

- These indications require smaller studies, but have potential for "orphan pricing"

7

Hematopoietic Cell Transplant (Bone Marrow Transplant [BMT])

Status: Preclinical studies ongoing

- Collaboration with Boston Children's on bone marrow transplantation in non-human primates

Next Steps: Proceed to develop Phase 2 study in BMT Recipients

α- CD40L for Sjögren's Syndrome

- Sjögren's is a **life-long autoimmune condition**, where tear and salivary glands are initially affected
- In 2019, there were an estimated **2.26 million prevalent cases** of primary Sjögren's syndrome worldwide. Forecasted to increase to 2.52 million prevalent cases by 2028

Horizon (acquired by Amgen) has announced two positive Phase 2 trial populations in Sjögren's Syndrome

September 12, 2022:

Horizon Therapeutics plc Announces Phase 2 Trial Evaluating Dazodalibep for the Treatment of Sjögren's Syndrome Meets Primary endpoint[1]

January 18, 2023

Horizon Therapeutics plc Announces Phase 2 Trial Evaluating Dazodalibep for the Treatment of Sjögren's Syndrome Meets Primary Endpoint in the Second Study Population; Only Phase 2 Trial to Meet Primary Endpoint in Both Patient Populations[2]

[1]https://www.biospace.com/article/releases/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-dazodalibep-for-the-treatment-of-sjoegren-s-syndrome-meets-primary-endpoint/
[2]https://www.businesswire.com/news/home/20230118005359/en/Horizon-Therapeutics-plc-Announces-Phase-2-Trial-Evaluating-Dazodalibep-for-the-Treatment-of-Sj%C3%B6gren%E2%80%99s-Syndrome-Meets-Primary-Endpoint-in-the-Second-Study-Population-

Sanofi's Frexalimab α-CD40L Missed in Sjögren's Syndrome

- Sanofi reported that their Fc-modified anti-CD40L mAb (frexalimab) missed in Sjögren's Syndrome[1] (also attached) and that their Sjögren's program has been abandoned
  - "Another high-profile compound, frexalimab, reached the end of the road in Sjögren's syndrome due to subpar efficacy. But the CD40L antibody, which has been touted as a 'pipeline-in-a-product,' continues to be developed in two different types of multiple sclerosis, type 1 diabetes as well as systemic lupus erythematosus."

- Frexalimab's miss in Sjögren's is in contrast to two positive Phase 2 studies in Sjögren's with Horizon/Amgen's dazodalibep (tn03 fusion protein)[2-4]
  - Note that dazodalibep is an albumin fusion protein with no Ig Fc functionality[4], so the deficiency of frexalimab seems to be specific to the combining site ($F(ab)_2$).
  - Frexalimab is derived from IDEC-131/toralizumab[5], from which it differs by a few aa substitutions in the CDRs to increase affinity.

[1]Tong, A. April 25, 2024. Endpoints. "Sanofi spotlights early-stage cancer assets, counts on grandfather clause on Biosecure"
[2]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating
[3]https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-announces-phase-2-trial-evaluating-0
[4]Karnell JL, et al. *Sci Transl Med.* 2019. 11(489):eaar6584. doi: 10.1126/scitranslmed.aar6584. PMID: 31019027.
[5]Fadul CE, et al. *Neurol Neuroimmunol Neuroinflamm.* 2021 Oct 15;8(6):e1096. doi: 10.1212/NXI.0000000000001096. PMID: 34654708; PMCID: PMC8527364.

TNX-1500: Key Considerations

- TNX-1500 may be used in large markets that are not currently well served
- There is a long history of use of monoclonal antibodies
- Tonix has engineered a potentially more active and better tolerated molecule than previous anti-CD40L mAbs
- Intellectual property filed (composition of matter)

Key milestones:

- Phase 1 study PK completed
- Autoimmune disorders – Planning INDs

TNX-1500 (α-CD40 Ligand)
Market Opportunity

OPPORTUNITY

Organ transplant rejection drugs	Kidney transplants: 24,000/year/US[2]	Autoimmune Lupus: 1.5 M patients in US[4]	Autoimmune Disease
$4.7 billion[1]	**$5.54 billion[3]**	**$1.87 billion[5]**	**$149.4 billion[6]**

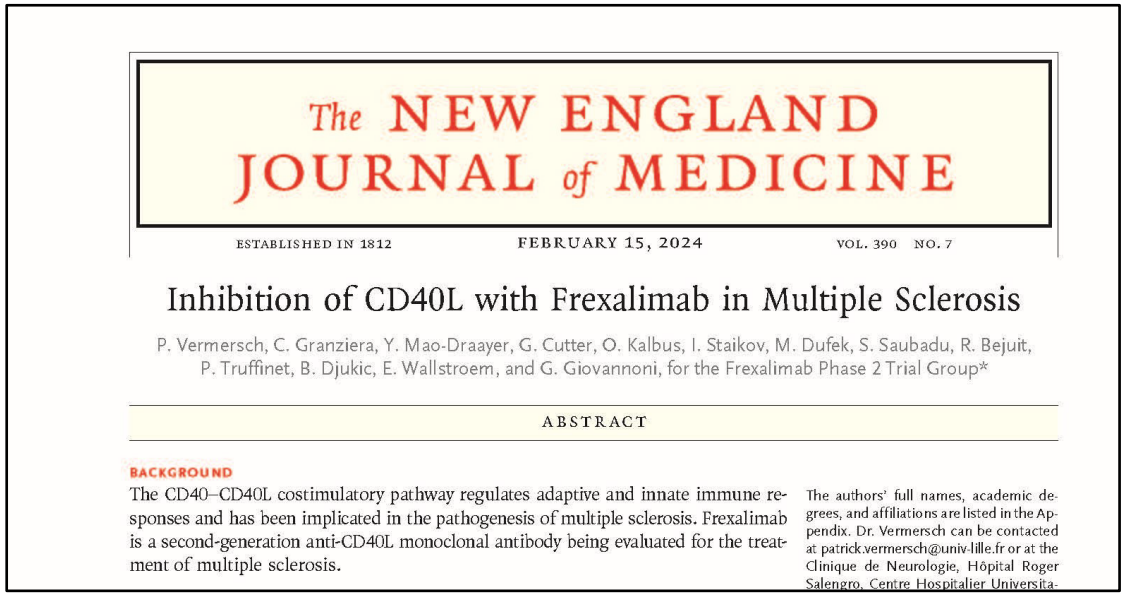
[1]Global market as of 2018 (https://www.biospace.com/article/organ-transplant-rejection-medications-market-drug-companies-focus-on-improving-long-term-outcome-of-new-drugs/)
[2]Wang, Jeffrey H. and Hart, Allyson. *Kidney360* November 2021; 2(11) 1836-1839
[3]Global market as of 2020 (https://www.grandviewresearch.com/industry-analysis/transplantation-market)
[4]https://www.lupus.org/resources/lupus-facts-and-statistics
[5]Global market as of 2020 (https://www.globenewswire.com/news-release/2021/02/18/2177637/0/en/Global-Lupus-Therapeutics-Market-Is-Expected-to-Reach-USD-3-62-Billion-by-2028-Fior-Markets.html)
[6]Anticipated market size by 2025 (https://www.prnewswire.com/news-releases/the-global-autoimmune-disease-therapeutics-market-size-is-expected-to-reach-149-4-billion-by-2025--rising-at-a-market-growth-of-4-34-cagr-during-the-forecast-period-300902336.html)

TONIX PHARMACEUTICALS

α-CD40L Headlines

- Sanofi recently published their Phase 2 data on frexalimab in multiple sclerosis in the the *New England Journal of Medicine*[1]
  - Sanofi projects its Fc-modified humanized anti-CD40L mAb frexalimab will exceed €5 B per year in peak sales[2]

- Like frexalimab, TNX-1500 is Fc-modified to reduce/eliminate the risk of thrombosis seen with "first generation" anti-CD40L mAbs



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Inhibition of CD40L with Frexalimab in Multiple Sclerosis

P. Vermersch, C. Granziera, Y. Mao-Draayer, G. Cutter, O. Kalbus, I. Staikov, M. Dufek, S. Saubadu, R. Bejuit, P. Truffinet, B. Djukic, E. Wallstroem, and G. Giovannoni, for the Frexalimab Phase 2 Trial Group*

ABSTRACT

BACKGROUND

The CD40–CD40L costimulatory pathway regulates adaptive and innate immune responses and has been implicated in the pathogenesis of multiple sclerosis. Frexalimab is a second-generation anti-CD40L monoclonal antibody being evaluated for the treatment of multiple sclerosis.

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Dr. Vermersch can be contacted at patrick.vermersch@univ-lille.fr or at the Clinique de Neurologie, Hôpital Roger Salengro, Centre Hospitalier Universita-

"1200 mg of frexalimab administered intravenously every 4 weeks (with an 1800-mg loading dose), 300 mg of frexalimab administered subcutaneously every 2 weeks (with a 600-mg loading dose), or the matching placebos for each active treatment."

Interpretation: Doses correspond approximately (for a 60 kg human) to ~20 mg/kg *i.v.* q 4 weeks, with a ~ 30 mg/kg loading dose, or ~ 5 mg/kg *s.c.* q 2 weeks with a ~ 10 mg loading dose.

[1]Vermersch P, et al. N Engl J Med. 2024 Feb 15;390(7):589-600. doi: 10.1056/NEJMoa2309439. PMID: 38354138

[2] Dunn, A. Endpoints. December 7, 2023. "Sanofi CEO Paul Hudson pitches 12 blockbusters in a bid to convince investors on boosting R&D spend".https://endpts.com/sanofi-rd-day-ceo-paul-hudson-touts-12-blockbusters-ups-rdspend/

Recent mAb Transactions

2020 October

Momenta acquired by Johnson & Johnson for $6.5B[1]

- Nipocalimab (M281) is a clinically validated anti-FcRn antibody with a rare pediatric disease designation from the US FDA
- J&J called nipocalimab “a pipeline in a product”

2021 March - April

Kymab acquired by Sanofi for $1.1B[2]

- mAb anti-Ox40L for the treatment of autoimmune disease

Viela Bio acquired by Horizon for $3B[3]

- UPLIZNA® (inebilizumab-cdon) is an anti-CD19 (B-cell-depleting) antibody approved for the treatment of neuromyelitis optica spectrum disorder (NMOSD), which is a rare and severe autoimmune disease
- VIB4920 anti-CD40L is Viela’s second program

2022 March

Sanofi and IGM Biosciences announce collaboration deal that could surpass $6B[4]

- The two companies will partner on immunoglobulin M (IgM) antibody agonists against three cancer targets and three immunology/inflammation targets

Merck announces plan to acquire Prometheus for $10.8B[5]

- Two mAbs targeting TNF family members:TL1A (PRA-023) and CD30L (PRA-052) for the treatment of inflammatory bowel disease and other autoimmune conditions

2023 April - October

Horizon acquired by Amgen for $27.8B[6] – Lead Drugs:

- Krystexxa® (pegloticase) - Gout
- Tepezza® (teprotumumab) mAb anti-IGF-1R – Grave’s Disease
- Dazodalibep (tn03 fusion protein) Anti-CD40L – Sjögren's Syndrome

Sanofi and Teva to co-develop anti-TL1A in $1.5B deal[7]

- Anti-TL1A mAb for inflammatory bowel disease

[1]Johnson & Johnson. October 1, 2020. Accessed June 3, 2021. https://www.jnj.com/johnson-johnson-completes-acquisition-of-momenta-pharmaceuticals-inc

[2]Sanofi. April 9, 2021. “Sanofi completes Kymab acquisition. www.sanofi.com/en/media-room/press-releases/2021/2021-04-09-05-00-00-2207173.

[3]Horizon. March 15, 2021. “Horizon Therapeutics plc completes acquisition of Viela Bio, Inc. https://ir.horizontherapeutics.com/news-releases/news-release-details/horizon-therapeutics-plc-completes-acquisition-viela-bio-inc

[4]BioSpace. March 29, 2022. Accessed March 29, 2022. https://www.biospace.com/article/sanofi-and-igm-partner-on-oncology-and-immunology-in-deal-worth-more-than-6-billion/

[5]April 16, 2023. Merck. “Merck strengthens immunology pipeline with acquisition of Prometheus Biosciences” www.merck.com/news/merck-strengthens-immunology-pipeline-with-acquisition-of-prometheus-biosciences-inc/

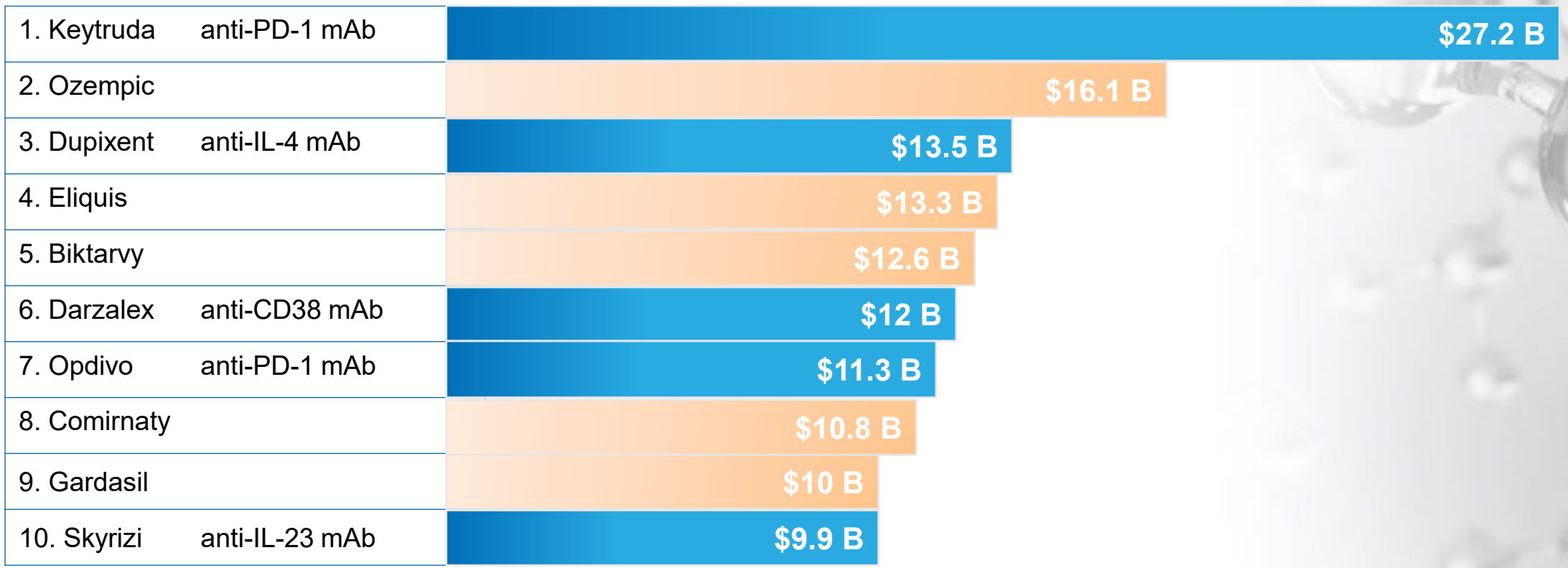
[6]Endpoints News. October 6, 2023. “Amgen closes $28B Horizon acquisition a month after FTC battle ended.” https://endpts.com/breaking-amgen-seals-28b-horizon-acquisition-a-month-after-ftc-battle-ended/

[7]BioSpace. October 4, 2023. “Sanofi, Teva Ink Potential $1.5B Deal Aimed at Blockbuster IBD Drug”. https://www.biospace.com/article/sanofi-teva/

mAbs Represent 5 of Top 10 Products by 2024 Projected Sales

- Over 100 mAbs have been approved by the US FDA, and significant growth potential remains[1]
- The global monoclonal antibodies market size was estimated at $238 B in 2023[2]

TOP 10 DRUGS WORLDWIDE BASED ON 2024 PROJECTED SALES[3]



[1]Mullard A. May 5, 2021. Accessed February 24, 2022. (https://www.nature.com/articles/d41573-021-00079-7)
[2]BioSpace. March 22, 2024. Access March 7, 2024. (https://www.biospace.com/article/releases/monoclonal-antibodies-industry-is-rising-rapidly)
[3]Matej Mikulic. Statista. Jan 5, 2024. Accessed March 7, 2024. (https://www.statista.com/statistics/973523/top-drugs-by-year-on-year-sales-increase/)

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THANK YOU