

## Targeted Immunology CD40/CD40L Therapeutics

Transplantation | Autoimmunity | ALS

January 2023



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### Single Company Focus: Leveraging Validated Biology to Develop Best-in-Class Immune-Modulating Therapeutics



- CD40/CD40L pathway validated by extensive historical proof-of-concept data
- Tegoprubart was engineered to increase potency, half-life and manufacturability vs. other anti-CD40 approaches
- Targeting areas of high unmet need including organ transplantation and ALS

- **\$65.9M in cash** and cash equivalents (as of September 30, 2022)
- Expected sufficient to fund operations into 2024
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# Tegoprubart: Tegoprubart: Pipeline in a Product Opportunity With Transplantation as the Primary Focus

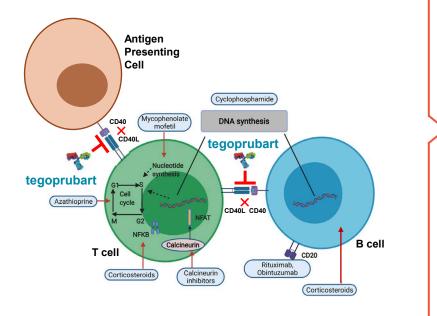
Product	Indication	Development Stage				Notes		
Candidate		Pre-clinical	Phase 1 Phase 2		Phase 3			
	Kidney Transplantation					<ul> <li>Phase 1b enrolling with interim data readout expected Q1 2023</li> <li>Phase 2 expected to launch mid-2023</li> </ul>		
	Liver Transplantation					Academic collaboration		
Tegoprubart	Xenotransplantation					eGenesis collaboration		
	Amyotrophic Lateral Sclerosis (ALS)					Phase 2 top-line reported May 2022		
	lgA Nephropathy					<ul><li>Program deprioritized</li><li>Interim safety data readout Q1 2023</li></ul>		
AT-2001	Autoimmune Indications							

Note: Development plans and timelines may change, including based on US and global regulatory interactions.



## Mechanism Overview of CD40L Inflammatory Signaling

### CD40/CD40L Pathway and Tegoprubart Site of Action



- Interaction of CD40 with CD40L on immune cells mediates activation of the co-stimulatory immune pathway, controlling "cross talk" between the adaptive and innate immune systems
- Maximal activation of inflammatory system is a 3-step process requiring co-stimulatory signaling
  - Step 1: Major histocompatibility complexes (MHC) and CD3/TCR engagement
  - Step 2: CD40 and CD40L binding resulting in cell division and clonal expansion
  - Step 3: Pro-inflammatory response by polarized T cells expressing inflammatory chemokines and cytokines
- Blocking CD40L shifts polarization away from proinflammatory signaling to T cell anergy, apoptosis, and polarization to a Treg environment
  - Blocking CD40L thus does not generally result in lymphopenia often seen with immunosuppressive agents



## Tegoprubart: Potential Best-in-Class Anti-CD40/CD40L Antibody

Targetir	ng CD40 Ligand vs. CD40 Receptor	IgG1 vs. fusion protein or pegylated				
CD40L and CD40	CD40L only	FAB				
Targeting both anti- CD40L and anti-	<ul> <li>Blocking anti-CD40L also inhibits CD11 costimulatory receptors on antigen presenting cells, thus blocking the pro-inflammatory polarization of CD8<sup>+</sup> Cytotoxic T cells</li> </ul>	✓ Up to over 2x times longer half-life				
CD40 inhibits B cell polarization and class switching, as well as inhibits the pro- inflammatory	<ul> <li>Blocking CD40L also polarizes CD4<sup>+</sup> lymphocytes to FoxP3<sup>+</sup> Regulatory T cells (Tregs), thus creating a potentially more tolerogenic environment</li> </ul>	<ul> <li>Manufacturing advantages</li> </ul>				
polarization of CD4 <sup>+</sup> Helper T cells	<ul> <li>CD40L is more selectively expressed, providing the potential for additional safety and PK/PD/dosing advantages</li> </ul>	<ul> <li>Less anti-drug antibodies</li> </ul>				



## **Tegoprubart Experience**

# Tegoprubart Phase 1a/1b Single Ascending Dose Trial Completed in Healthy Subjects and ALS Patients

### Healthy Volunteers or ALS Patients Receiving Either tegoprubart (mg/kg, IV) or Placebo

Subjects	Healthy	Healthy	ALS	Healthy	Healthy	Healthy	Tego- prubart	Placebo
Dose (mg/kg)	0.5	1	1	2	4	8	NA	NA
n=	6	3	3	3	3	6	24	8

Number of Subjects (%) Experiencing TEAEs by Maximum Toxicity Grade								
Grade 1 (% Subjects Experiencing Events)	3 (50.0%)	2 (66.7%)	2 (66.7%)	2 (66.7%)	1 (33.3%)	1 (16.7%)	11 (45.8%)	5 (62.5%)
Grade 2 (% Subjects Experiencing Events)	-	_	1 (33.3%)	_	_	1 (16.7%)	2 (8.3%)	_
Grade 3	-	—	_	—	—	_	_	_
Grade 4	-	_	_	—	_	_	_	_
Grade 5	-	—	_	—	—	_	—	—



## Phase 2a ALS: Trial Design, Safety & Tolerability

#### Trial design:

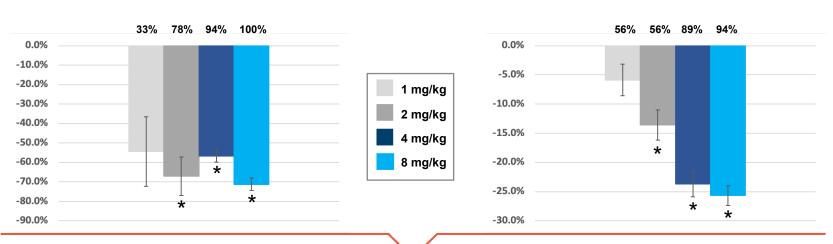
- 12-week, open label, multiple ascending dose level study
- Four sequential dose cohorts of 9 participants (1 and 2 mg/kg) and 18 participants (4 and 8 mg/kg) each
- Each participant serves as own control by comparing biomarker changes over time from initial baseline assessment

#### Safety & Tolerability:

- 35.2% of participants had 1 or more drug-related adverse events (AEs)
  - No drug-related serious or severe AEs
  - Occurrence of drug-related adverse events was balanced across dose cohorts
  - No thrombosis or signs of platelet activation
  - 2 participants experienced adverse events leading to withdrawal
    - 1 participant withdrew because of worsening depression in the 1 mg/kg cohort
    - 1 participant withdrew because of malaise in the 2 mg/kg cohort
- Anti-Drug Antibodies detected in ~4.2% of samples
  - ADAs were of low titer and did not effect tegoprubart levels



## Phase 2a ALS: Tegoprubart Demonstrates Dose Dependent T and B Cell Target Engagement



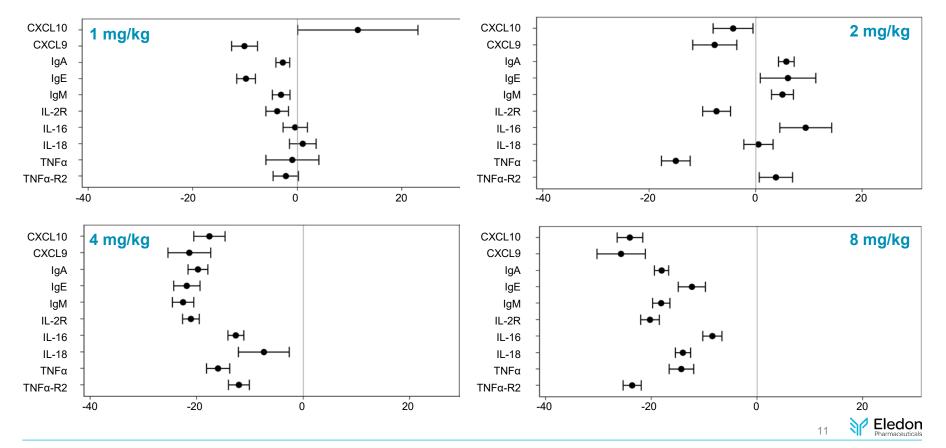
CD40L Change at Week 12 (%)

CXCL13 Change at Week 12 (%)

- Tegoprubart exposure decreased inflammatory biomarker levels in a dose dependent manner
- 20 biomarkers detected were statistically significantly reduced at one or both of the higher dose levels, including: IgA, IgE, IgM, C3, CXCL9 & CXCL10
- Target engagement at 12 weeks increased with dose



### Phase 2a ALS: Tegoprubart Demonstrates Dose Dependent Reduction in Pro-Inflammatory Biomarkers



Kidney Transplantation Opportunity & Clinical Development Plan

## Kidney Transplantation Overview

### **Unmet Need**

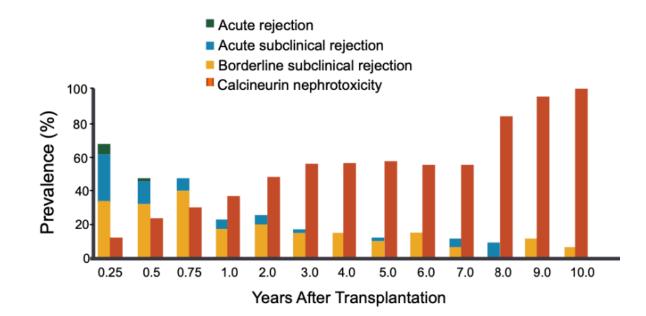
- In the 1990s, Calcineurin inhibitors (CNIs) revolutionized the field of transplantation, allowing transplant medicine to grow across transplant types, and providing meaningful treatment to thousands of people
- CNIs provide excellent 1 year patient and graft outcomes, but:
  - They are less effective against long term antibody mediated rejection
  - They are nephrotoxic and slowly harm the graft over time
  - They are associated with significant adverse effects including post-transplant new onset diabetes, tremors, and hair loss
- On average, transplanted kidneys from deceased donors function about 10 years

### **Market Size**

- 24,000+ U.S. kidney transplants per year
- 240,000+ Americans living with a kidney graft
- ~90,000 Americans face a 3-5 year wait for a kidney
  - ~5,000 Americans per year on the transplant waiting list die without getting a transplant
- Pre-transplant dialysis costs over \$100,000 per year
  - Hemodialysis has a 15-20% first-year mortality rate with a 5-year survival rate of under 50% (vs. ~80% 5-year survival post kidney transplant)
- Annual medical cost to treat transplant patients who experience renal graft failure increase 450%



# CNI Nephrotoxicity Over Time is a Leading Cause of Long-Term Kidney Transplant Graft Failure



At 6 months post transplant:

- ~24% of CNI treated patients demonstrate kidney impairment
- Up to 1/3 of CNI treated patients experience New Onset Diabetes After Transplant (NODAT) or impaired fasting glucose levels, which may also negatively impact kidney grafts over time

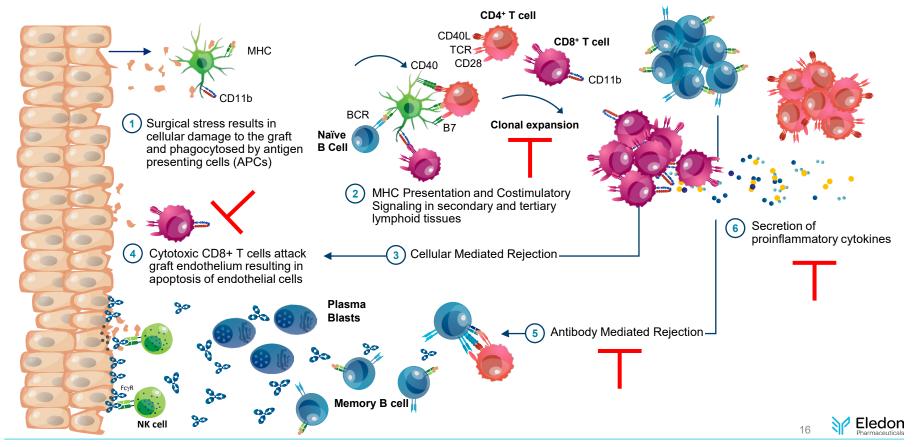


### Incidence of CNI Related Nephrotoxicity Increases with Time Post Transplant Across Organ Types

Organ Transplant	Duration of CNI Exposure (Years)	<b>CNI Nephrotoxicity</b> (defined as decreased kidney function / histology)		
Kidney-Pancreas	1 5 10	30% 55% 100%		
Liver	4 5	16% 18%		
Bone Marrow	8	67%		
Heart	5 10	9% 9% ESRD		
Lung	5	14%		
Intestine	5	21%		

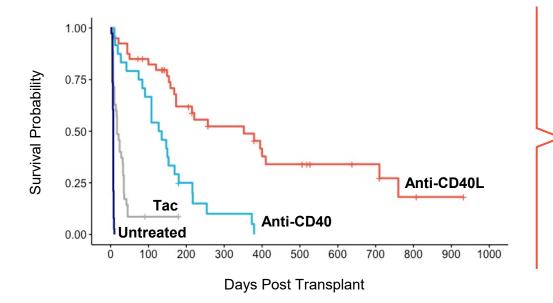


### Anti-CD40L in the Prevention of Transplant Rejection



### Inhibition of CD40L Improved Survival vs. CD40 Inhibition in Non-Human Primate (NHP) Kidney Transplantation Monotherapy Studies

**NHP Survival Post Kidney Transplant** 

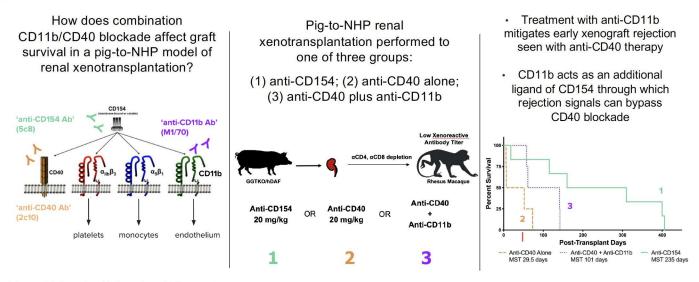


In aggregated data from published studies, NHPs receiving anti-CD40L (e.g., 5c8, AI794, IDEC-131) immunomodulation monotherapy post kidney transplantation had longer average survival than those receiving anti-CD40 monotherapy (e.g., 4D11, cH5D12, Chi220, ASKP1240, tacrolimus monotherapy or untreated controls



# Recent NHP Experience has Demonstrated Advantage of Blocking CD40L vs. CD40R in Xenotransplantation

Combined CD11b/CD40 Blockade is Superior to CD40 Blockade Alone in Prolonging Survival in Pig-to-Nonhuman Primate Renal Xenotransplantation



Emory University, University of Minnesota; Faber, Lovasik, Matar, Breeden, Kim, Adams

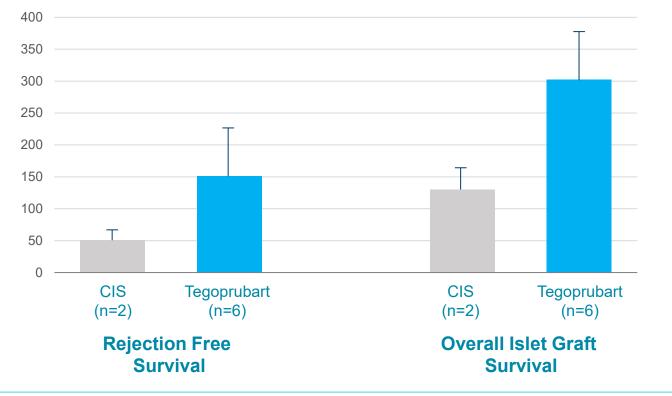
Abstract number 2





Tegoprubart Prolonged Graft Survival vs. CNI Containing Regimen (CIS) in a Non-Human Primate Islet Cell Transplant Model...

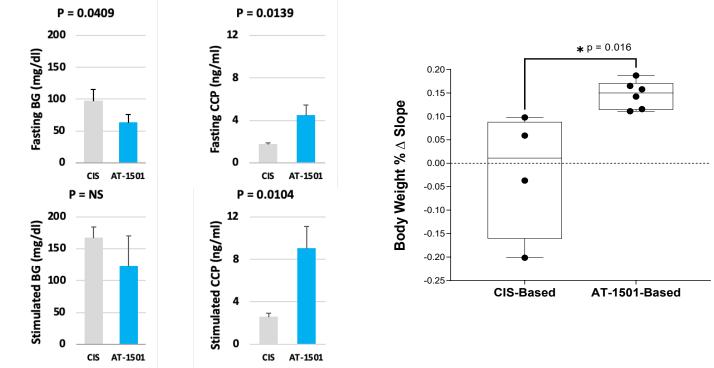
### Mean Survival (Days)





... And Tegoprubart was Associated With Better Metabolic Control as Well as Healthier Animals Overall as Demonstrated by Body Weight

Tegoprubart (AT-1501) vs. CNI Regimens (CIS) in NHP Islet Cell Transplantation Model





## Phase 1b Kidney Transplantation Study Design

#### DESIGN

- 52-week, open label, single dose level study
- Up to 12 participants undergoing kidney transplantation at multiple sites in Canada, the United Kingdom and Australia
- Kidney transplant using standard induction therapy plus maintenance therapy with tegoprubart as a replacement for CNIs (tacrolimus)

### PLANNED DATA GENERATION

- Safety & tolerability
- PK/PD
- Graft survival & function
- Biopsy proven acute rejection
- Immune cell infiltrate of graft biopsy
- Biomarker measures of kidney injury and rejection risk

## This study will run in parallel to the Phase 2 clinical trial of tegoprubart in kidney transplantation

Note: Development plans may change, including based on US and global regulatory interactions



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## Phase 2 BESTOW Kidney Transplantation Study Design

#### DESIGN

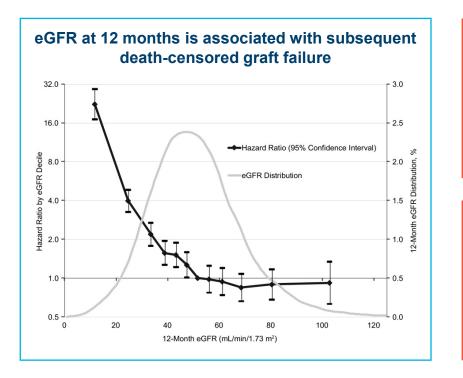
- 52-week, head-to-head, superiority trial, open label, 2-arm, active comparator safety, PK, and efficacy study
- Approximately 120 participants (60/arm) undergoing kidney transplantation at multiple sites in the United States and other countries
- Participants will receive tegoprubart or the active comparator, tacrolimus, as part of an immunosuppressive regimen including corticosteroids and mycophenolate mofetil (MMF) or mycophenolate sodium (MPS)

### PLANNED DATA GENERATION

- Safety & tolerability
- Graft function (eGFR)
- Rates of graft functional impairment
- Biopsy proven acute rejection (BPAR)
- Rate of new onset diabetes mellitus (NODAT)
- Rate of participant and graft survival
- PK and immunogenicity



### Kidney Allograft Function is an Early Predictor of Future Graft Failure



- Graft function measured using eGFR at 12 months post transplant is associated independently with subsequent graft failure
- Of multiple covariates,12-month eGFR is the strongest predictor of graft failure



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## **Eledon Pharmaceuticals**

19900 MacArthur Blvd., Suite 550 Irvine, California 92612, USA info@eledon.com +1 949-238-8090

