



**ZIOPHARM Oncology**

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# **NIH OBA Protocol #1310-1262 (ATI001-102) RAC Public Review Slides**

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December 4, 2013

# ZIOPHARM & Invited Experts:

## ZIOPHARM:

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SVP, Clinical Development &  
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## Invited Experts:

John Nemunaitis, MD  
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Chairman, Department of Neurosurgery  
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# Agenda

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- High Grade Gliomas
- Inducible Ad-RTS system
- Pre-clinical data (PK and Survival)
- Dose Justification for Phase 1 Glioma Protocol
  - Plasma / Brain (mouse model)
- Phase 1 Glioma Study Design
- Clinical Experience (Safety)

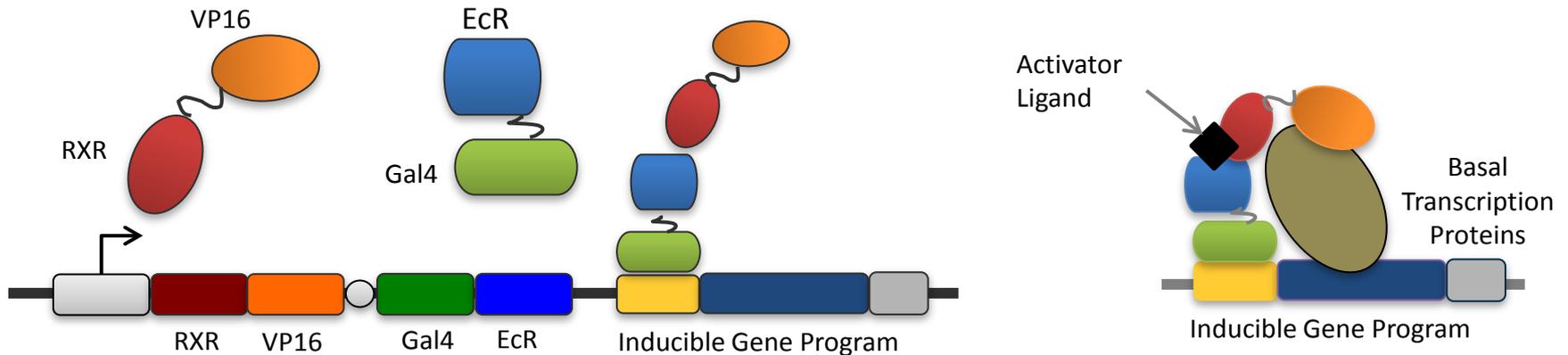
# High Grade Gliomas

- Most common primary malignant brain tumors
- 17,000 new cases per year; Poor prognosis and QOL
- Glioblastoma have 36% (1 yr) and 4.7% (5yrs) survival
- Neurosurgery for Dx biopsy, mass effect, cytoreduction
- First-line adjuvant treatment with Rx and temozolomide (Biodegradable polymer-carmustine, bevacizumab)
- Most patients have median PFS of 7-10 months before recurrence
- Treatment of recurrence include surgery, salvage chemotherapy with alkylating agents or bevacizumab
- After failure of above medium survival is 3-4 months

Modified after Omuro A. et al JAMA Nov 2013

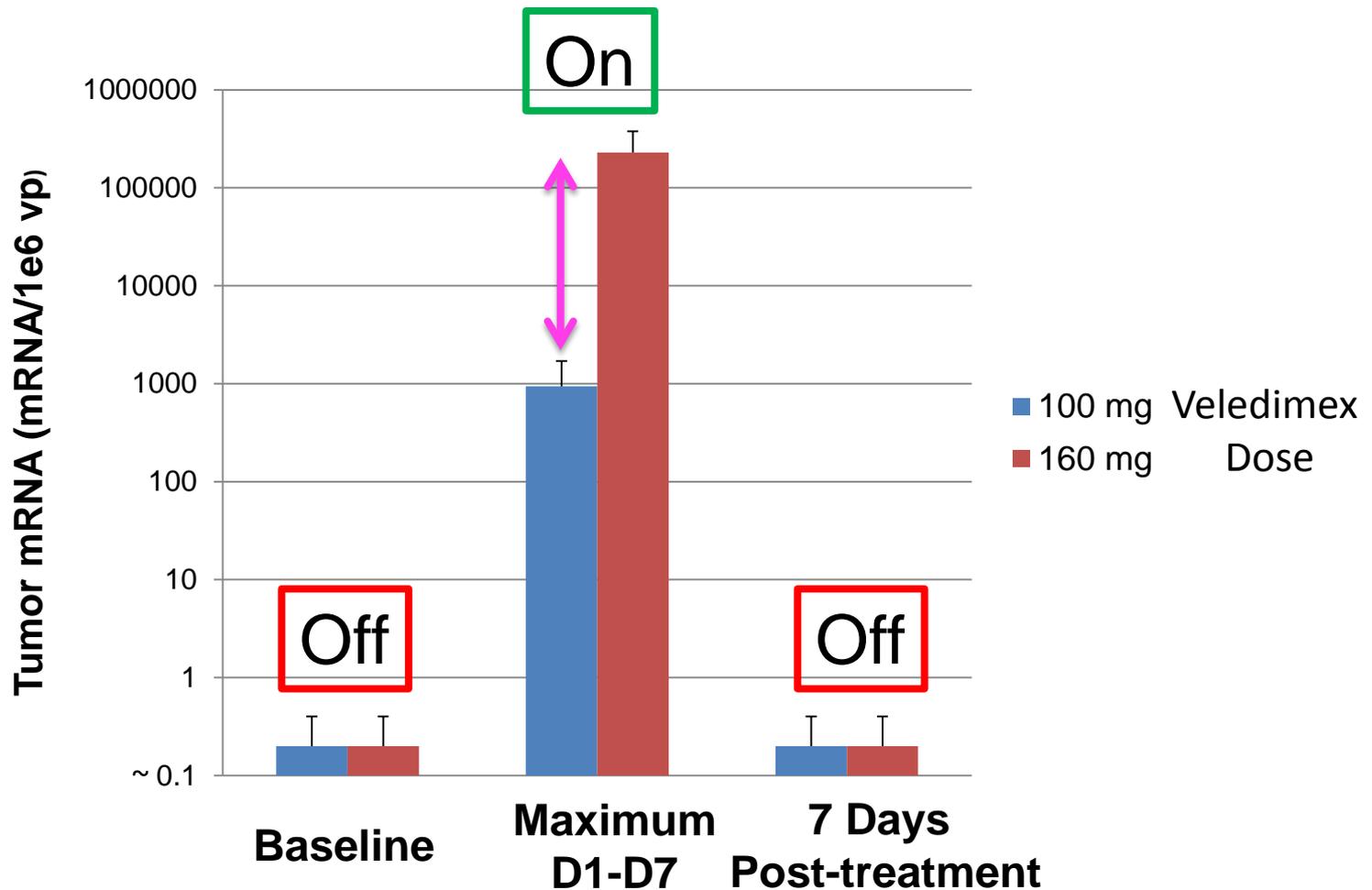
# Inducible Gene Regulation - RheoSwitch Therapeutic System®

RheoSwitch Therapeutic System® (RTS®) is a three-component transcriptional regulator



- 1. The Switch Components:** The RTS® gene program includes two receptor protein fusions: VP16-RXR and Gal4-EcR. They form unstable and unproductive heterodimers in the absence of any ligand.
- 2. The Activator Ligand:** An ecdysone analog, diacylhydrazine-based small molecule functions as an activator. In the presence of the ligand, the protein heterodimer changes to a stable conformation and binds to the inducible promoter.
- 3. The Inducible Promoter:** A customizable promoter to which basal transcription proteins are recruited and the target gene is transcribed.

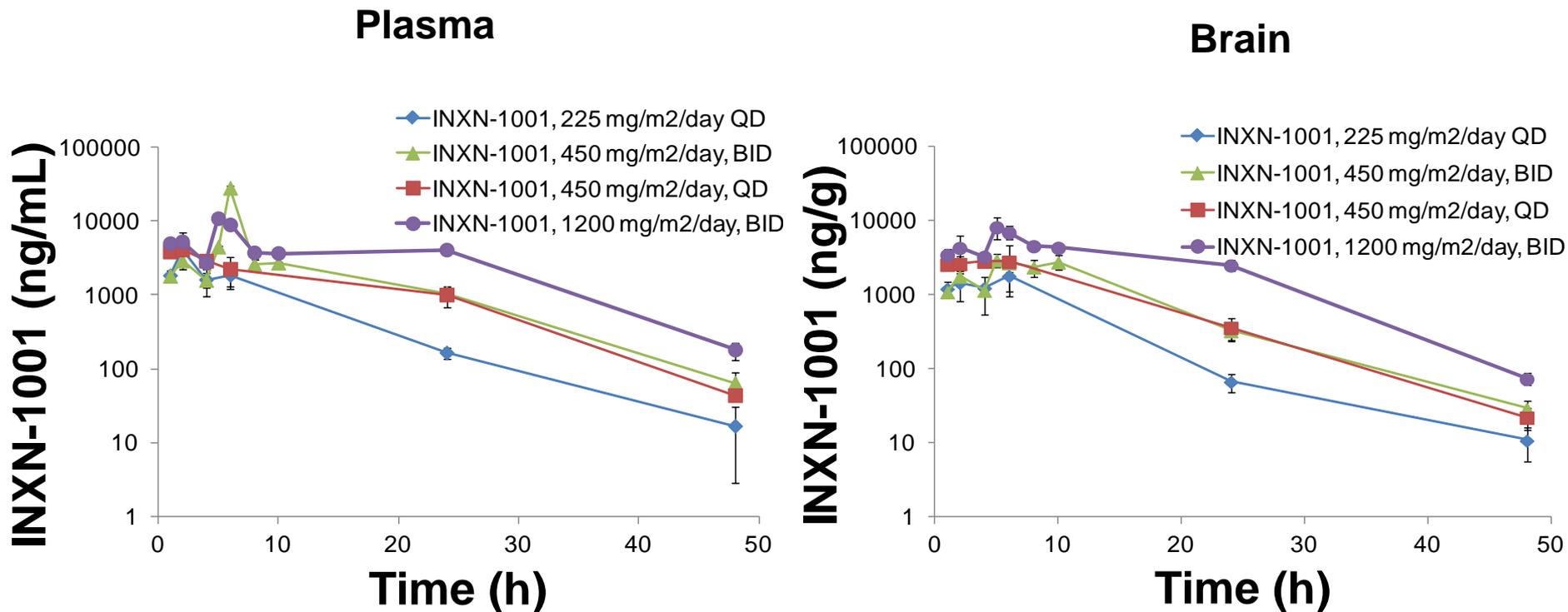
# Veledimex Tightly and Precisely Controls the Expression of IL-12 $\beta$ mRNA in the Tumor



## Nonclinical Summary

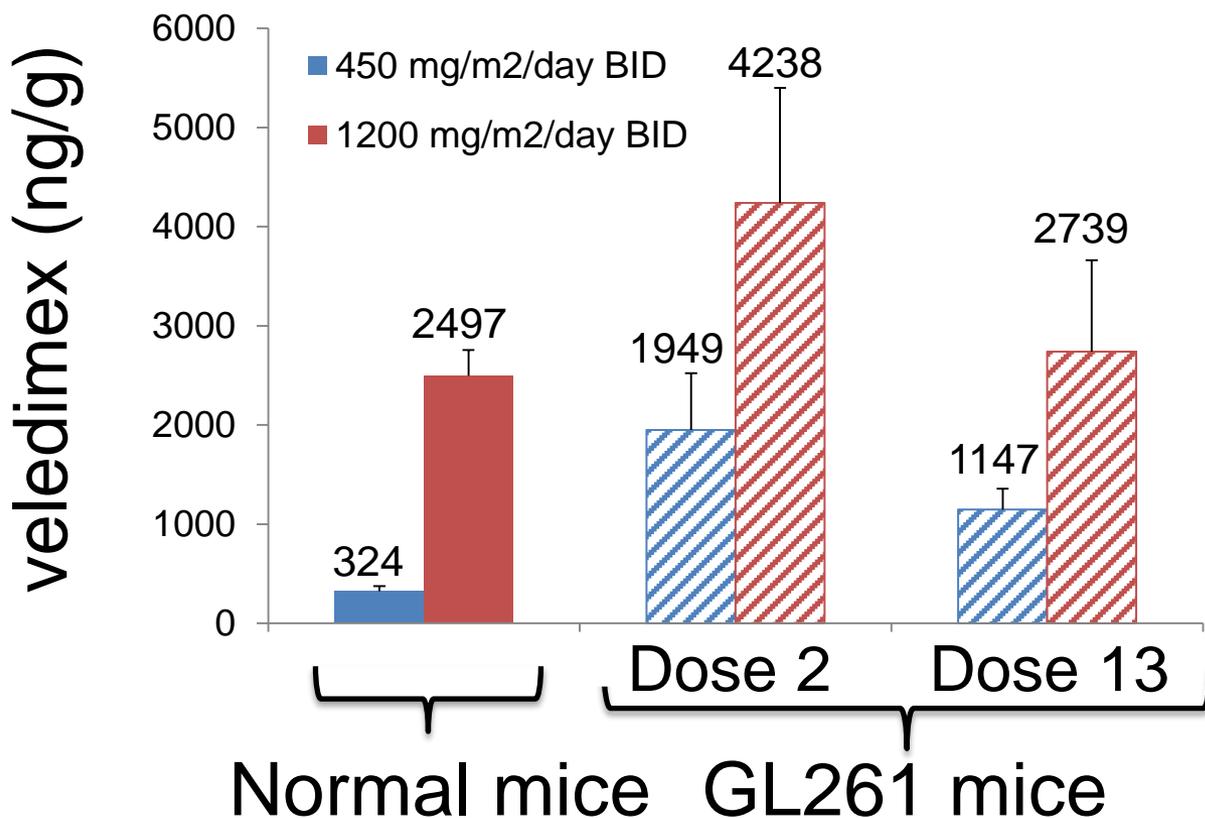
- Increasing tumor vector dose in the presence of veledimex 150 mg/m<sup>2</sup> elicited dose-related increases in IL-12 production. 5x10<sup>9</sup> -1x10<sup>10</sup> vp was chosen for all subsequent nonclinical work
- Orally administered veledimex resulted in:
  - dose-related increase in tumor veledimex levels
  - dose-related increase in expression of IL-12p70 in the tumor with minimal increase in serum IL-12
  - increase in tumor CD8+ cytotoxic T cells concomitant with a decrease in tumor Tregs
- Ad-RTS-mIL-12 + veledimex elicited dose-related decrease in tumor growth rate, with no significant change in body weight

# Plasma & Brain Tissue Profiles of Veledimex in C57BL/6 Mice



Veledimex exhibited dose-related increases in plasma & brain tissue exposure ( $AUC_{0-48}$ )

# Veledimex Levels at 24 h in Brain of Normal and GL261 Orthotopic Glioma Mouse Model

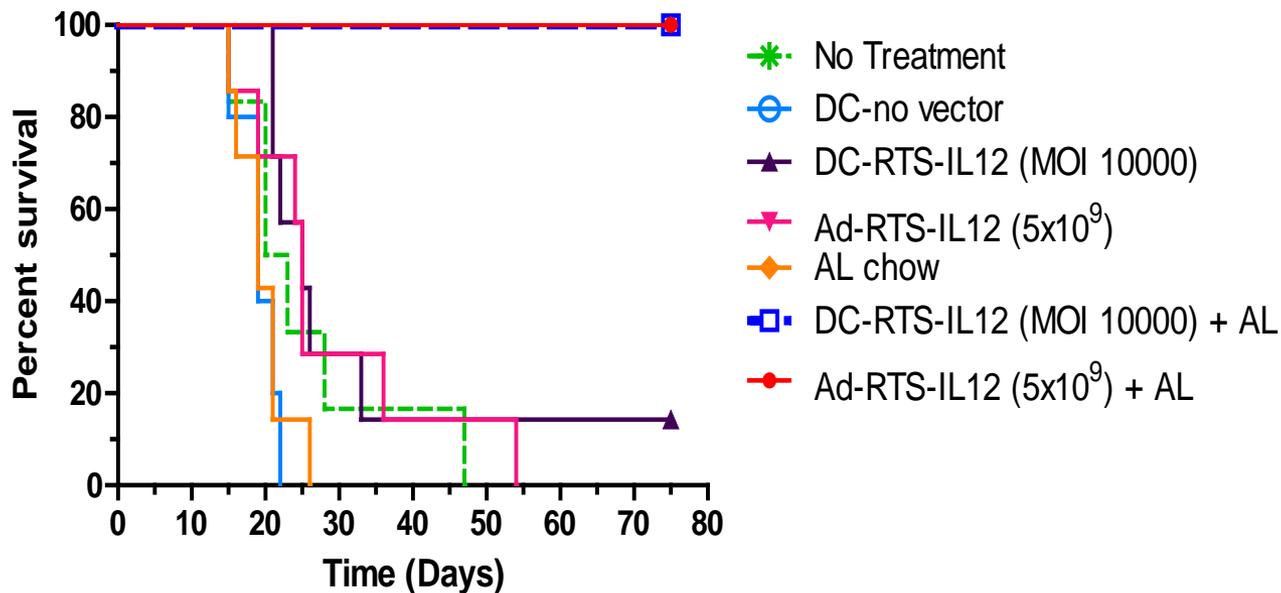


At 24 h veledimex brain concentration was approximately 1.7- and 6-fold higher in GL261 mice than in normal C57BL/6 mice at 1200 and 450 mg/m<sup>2</sup>/day doses, respectively. Normal mice received a single dose while GL-261 mice were dosed daily for 14 days

# Orthotopic Glioma Methods

- Each animal received  $1 \times 10^5$  GL261 glioma cells via intracranial injection (i.c.) 2mm from sagittal suture at a depth of 3mm. Untreated animals survive for 25 days
- On Day 5 animals (N=10 each) were administered transduced DC-RTS-IL-12 at  $1 \times 10^6$  cells/animal, i.t., or Ad-RTS-IL-12 at  $1 \times 10^8$ ,  $5 \times 10^8$ ,  $1 \times 10^9$ , or  $5 \times 10^9$  vp/animal, i.t.
- C57BL/6 murine dendritic cells were transduced at increasing multiplicity of infection (MOI) of 100, 500, 1000, 5000, or 10000 virus particles (vp)/cell
- Veledimex (AL) was administered *ad libitum* in the chow starting on Day 4 ( $\sim 675$  mg/m<sup>2</sup>/day) and continued for the duration of the study
- The endpoint was death due to disease progression

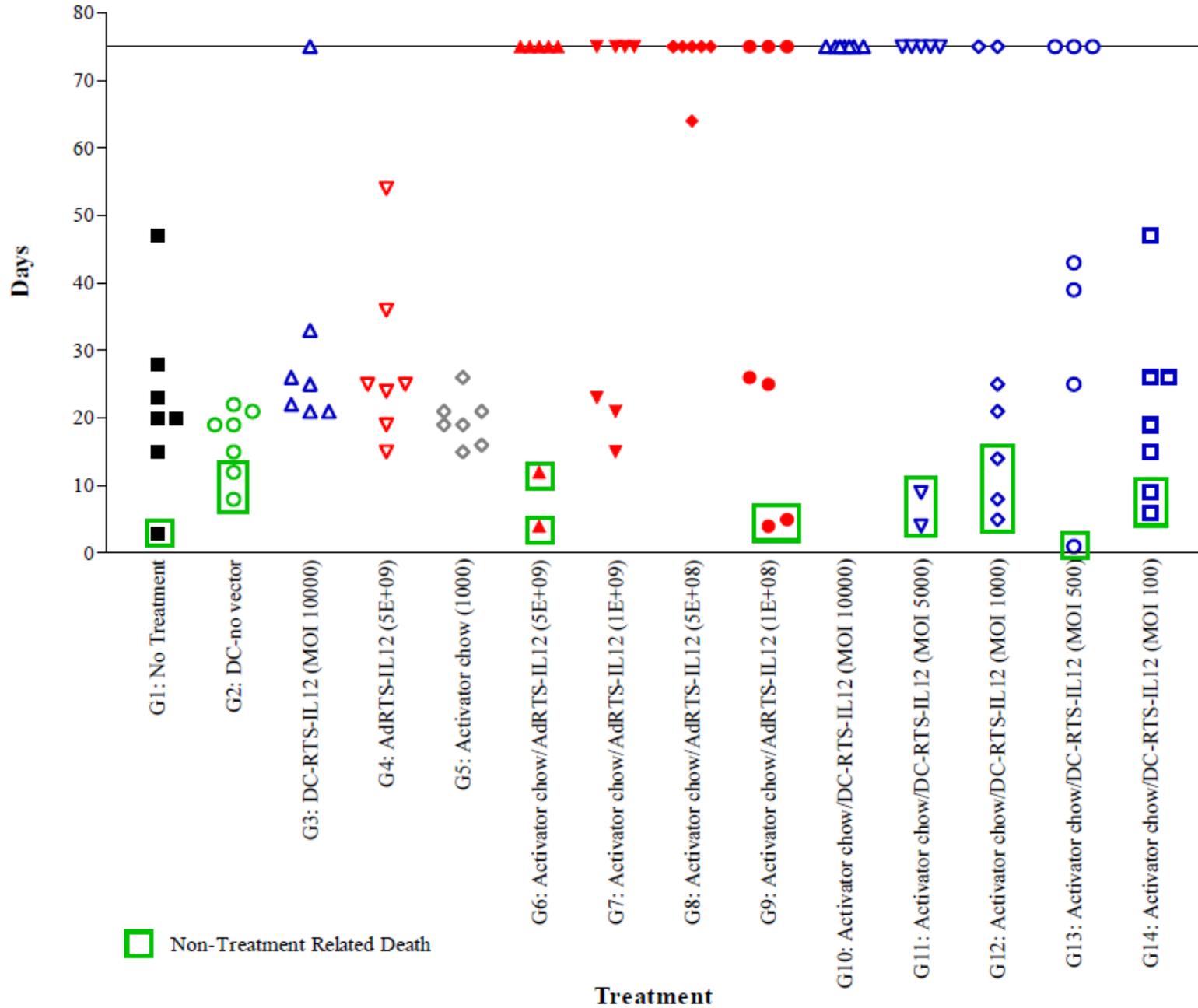
# Anti Tumor Activity of Ad-RTS-hIL-12 and Veledimex in the GL261 Glioma Model



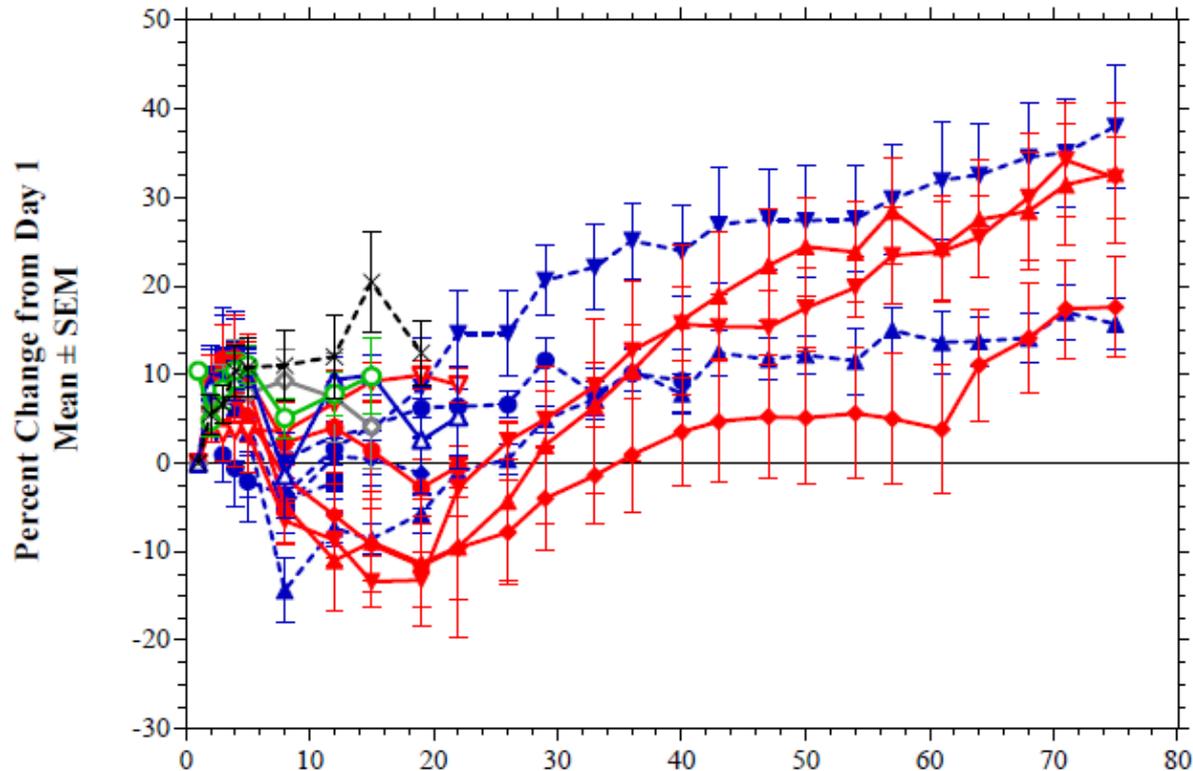
AL dosing Day 4 to EOS at  $\sim 675 \text{ mg/m}^2/\text{day}$  in chow; DC-RTS-IL12 or Ad-RTS-IL12 on Day 5

**100 % survival observed with either Ad-RTS-IL-12 + AL or DC-RTS-IL-12 + AL**

# Individual Times to Endpoints (TTE)



# Ad-RTS-IL-12 + AL and DC-RTS-IL-12 + AL Does Not Adversely Affect Body Weight



- x--- G1: No Treatment
- o--- G2: DC-no vector
- △--- G3: DC-RTS-IL12 (MOI 10000)
- ▽--- G4: AdRTS-IL12 (5E+09)
- ◇--- G5: Activator chow (1000)
- ▲--- G6: Activator chow/AdRTS-IL12 (5E+09)
- ▼--- G7: Activator chow/AdRTS-IL12 (1E+09)
- ◆--- G8: Activator chow/AdRTS-IL12 (5E+08)
- G9: Activator chow/AdRTS-IL12 (1E+08)
- ★--- G10: Activator chow/DC-RTS-IL12 (MOI 10000)
- ▽--- G11: Activator chow/DC-RTS-IL12 (MOI 5000)
- ◆--- G12: Activator chow/DC-RTS-IL12 (MOI 1000)
- G13: Activator chow/DC-RTS-IL12 (MOI 500)
- G14: Activator chow/DC-RTS-IL12 (MOI 100)

# Dose Justification

- In GL261 mice, brain tissue levels at 24 h increased with increasing doses
- Veledimex brain concentration (trough level at 24 h) was approximately 1.7- and 6-fold higher in GL261 mice than in normal mice at doses of 1200 and 450 mg/m<sup>2</sup>/day BID, respectively
- Veledimex brain exposure reached 80-100 % of plasma level
- No veledimex accumulation in GL261 mouse brain was observed after repeat dosing for 14 days
- No preferential brain tumor uptake when compared to ipsilateral side

# Starting Dose For Phase 1 Study

- **Recommended starting dose:**
  - 40 mg/ day as a divided dose of 20 mg BID
- **Assumptions:**
  - In mice, 15-30 mg/m<sup>2</sup> was the minimally effective dose level with no adverse clinical signs observed
  - Doses of 20 & 100 mg (11 & 53 mg/m<sup>2</sup>) in patients had biologic effects and were devoid dose-limiting toxicity
  - At 40 mg/day in 70kg human the resultant dose corrected for body surface area would be 21 mg/m<sup>2</sup>/day



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# Phase 1 Glioma Study Design

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# Phase 1 Trial

## Patient Population

- Recurrent or Progressive Glioblastoma or Grade III Malignant Gliomas

## Study Design

- Fixed Dose Ad-RTS-hIL12 ( $1 \times 10^{12}$  vp)
- Veledimex (activator ligand) dose escalation, 4 dose levels
- Standard 3 + 3 dose escalation design (min 3 and max 6 patients at each dose level)

## Primary Endpoint

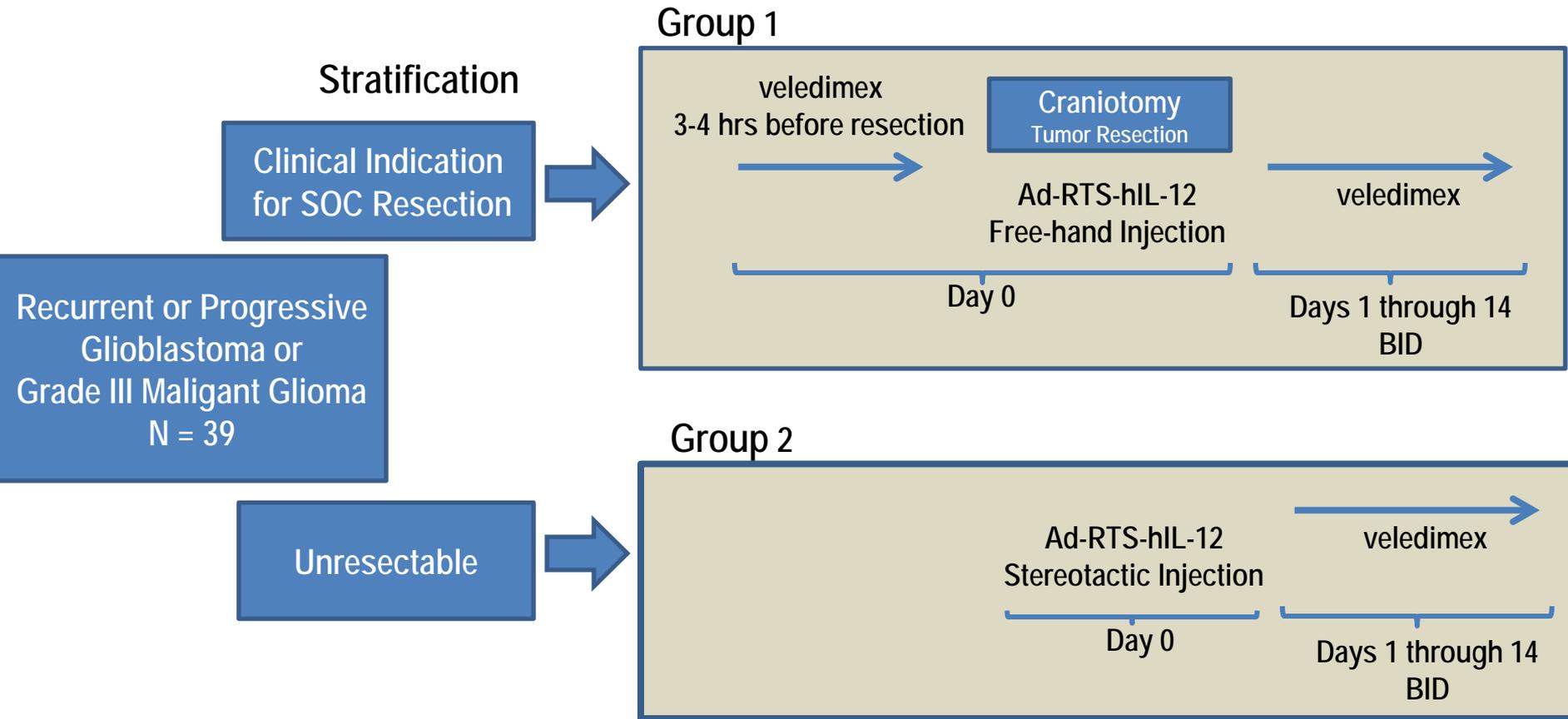
- Safety and tolerability of a single intratumoral Ad-RTS-hIL-12 dose plus escalating oral veledimex doses

## Secondary Endpoints

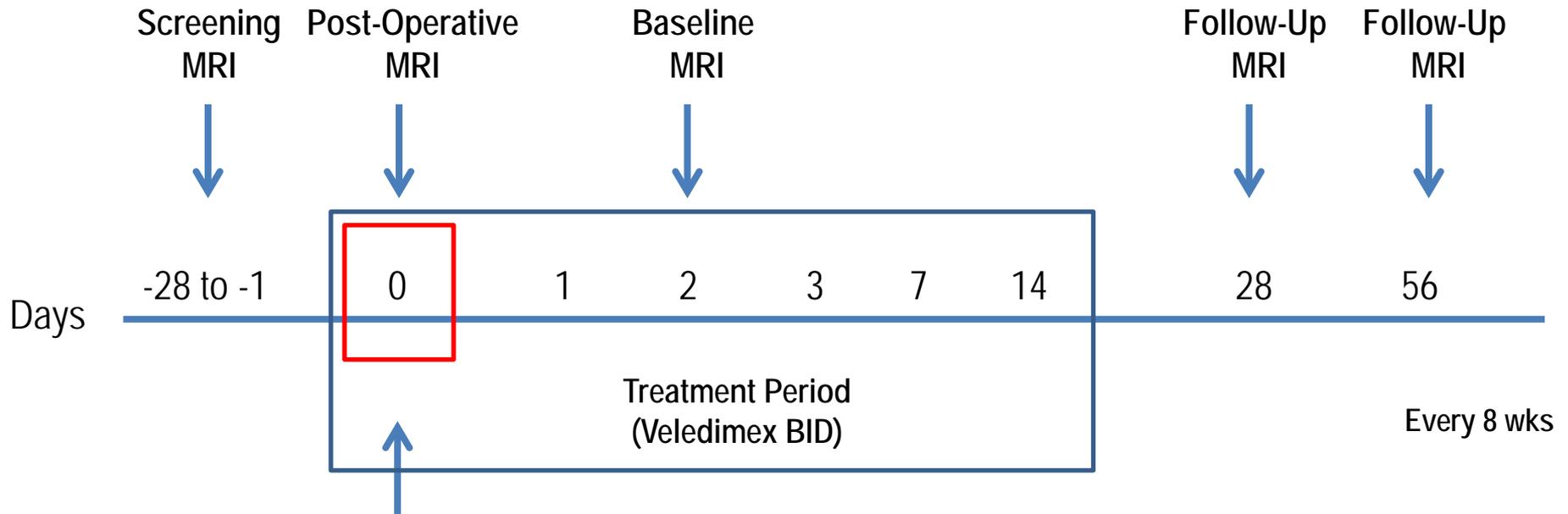
- Determine the veledimex PK Profile and MTD
- Evaluate cellular and humoral Immune Response
- Assess ORR, PFS and OS

# Phase 1 Study Design

## Ad-RTS-hIL12 + Veledimex Dose Escalation



# Schedule of Events



- PK / PD for Group 1
- Ad-RTS-hIL12 Injection
- First Veledimex Dose (12 hrs post Ad-RTS-hIL-12 injection)

# Key Inclusion / Exclusion Criteria

## Inclusion Criteria

- Histologically confirmed supratentorial glioblastoma or other WHO grade III or IV malignant glioma
- Evidence of tumor recurrence/progression by MRI (RANO criteria)
- Previous SOC treatment (surgery, post-operative radiotherapy and/or chemotherapy)
- Male or female subjects  $\geq 18$  and  $\leq 75$  years of age
- Karnofsky Performance Status  $\geq 70$

## Exclusion Criteria

- Prior immunotherapy
- Radiotherapy  $< 12$  weeks prior to starting the first veledimex dose
- Evidence of recent brain hemorrhage on screening MRI
- Evidence of clinically significant intracranial pressure, uncontrolled seizures, or need for immediate palliative treatment
- Use EIAED within 7 days prior to the first veledimex dose, other than levetiracetam (Keppra)

# Dose Escalation Schedule Phase 1

Cohort	Ad-RTS-hIL-12 (Day 0)	Veledimex (BID, Days 0 and 1-14)	
	Dose(vp)	Each Dose (mg)	Total Daily Dose (mg)
1	$\sim 1.0 \times 10^{12}$	20	40
2	$\sim 1.0 \times 10^{12}$	40	80
3	$\sim 1.0 \times 10^{12}$	60, 40	100
4	$\sim 1.0 \times 10^{12}$	60	120

Rationale for starting dose at 40mg/day:

- Nonclinical studies demonstrated that 15-30 mg/m<sup>2</sup> was the minimally effective dose level with no observed adverse clinical signs
- In our Phase 1 melanoma study dose of 20 and 100mg (11 & 53 mg/m<sup>2</sup>) had biologic effects and were devoid of dose-limiting toxicity

# On-going Melanoma and Breast Trials

## Overview of Treatment Emergent Adverse Events (TEAE)

Cohort	5 mg n = 3	20 mg n = 3	100 mg n = 3	140 mg n = 5	160 mg n = 8	160mg QOD n = 5
# Subjects with TEAE	3	3	3	4	8	4
# TEAE terms	45	20	58	59	215	73
# Related TEAE	23	11	47	33	149	44
# Subjects with SAEs	0	0	1	1	5	3
# SAE terms	0	0	2	1	12	9
# Related SAEs	0	0	0	1	10	6

- All data is from the CLINICAL database, unlocked
- SAE data is from the safety database, unlocked

# Melanoma Study ATI1001 - 101 Safety<sup>1</sup>

## ≥ Grade 3 related TEAEs (>5%)\*

AST elevation	19%
Hypotension	14%
Hyponatremia	9%
Leukopenia	9%
Pyrexia	9%

## Related SAEs (7 subjects)\*

Pyrexia (n=2), Hypotension (n=2), Mental Status Changes (n=2), Pancytopenia, Dehydration, Failure to Thrive, Febrile Neutropenia, Cytokine Release Syndrome, Neutropenia, Delirium, Anemia, Encephalopathy

\* All reverse on discontinuation of veledimex

<sup>1</sup>13Nov13 Datacut

# Conclusions

- Increased survival of GL-261 orthotopic glioma model with Ad-RTS-IL-12 + veledimex treatment
- Conservative starting dose to maximize patient safety
- Human PK and brain tumor tissue will allow informed dose adjustment
- Experience from on-going trials will guide safety monitoring
- Veledimex brain penetration established in mice and monkeys with intact blood brain barrier
- Inducible and controlled expression of IL-12 and compelling findings warrants translation into clinical Phase 1



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**THANK YOU**