NYU Langone Health

Zoster Eye Disease Study (ZEDS) Results

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Purpose of ZEDS

- To find out whether or not 12 months of low dose valacyclovir treatment, compared with placebo, delays time to development of new or worsening of specific eye disease manifestations of Herpes Zoster Ophthalmicus (HZO)

- Secondary objective: To find out whether there is persistent treatment benefit at 18 months, 6 months after cessation of treatment

- Participants were randomly assigned to valacyclovir or placebo in 4 groups
  - Age of *onset* of HZO: younger < 60 years vs older ≥ 60 years
  - Time since onset at *enrollment*: recent < 6 months vs chronic ≥ 6 mos

  - Rationale for groups
    - Expected ~50% < 60, disease manifestations vary by age
    - Expected greater benefit in recent onset disease

Second Aim: Postherpetic Neuralgia

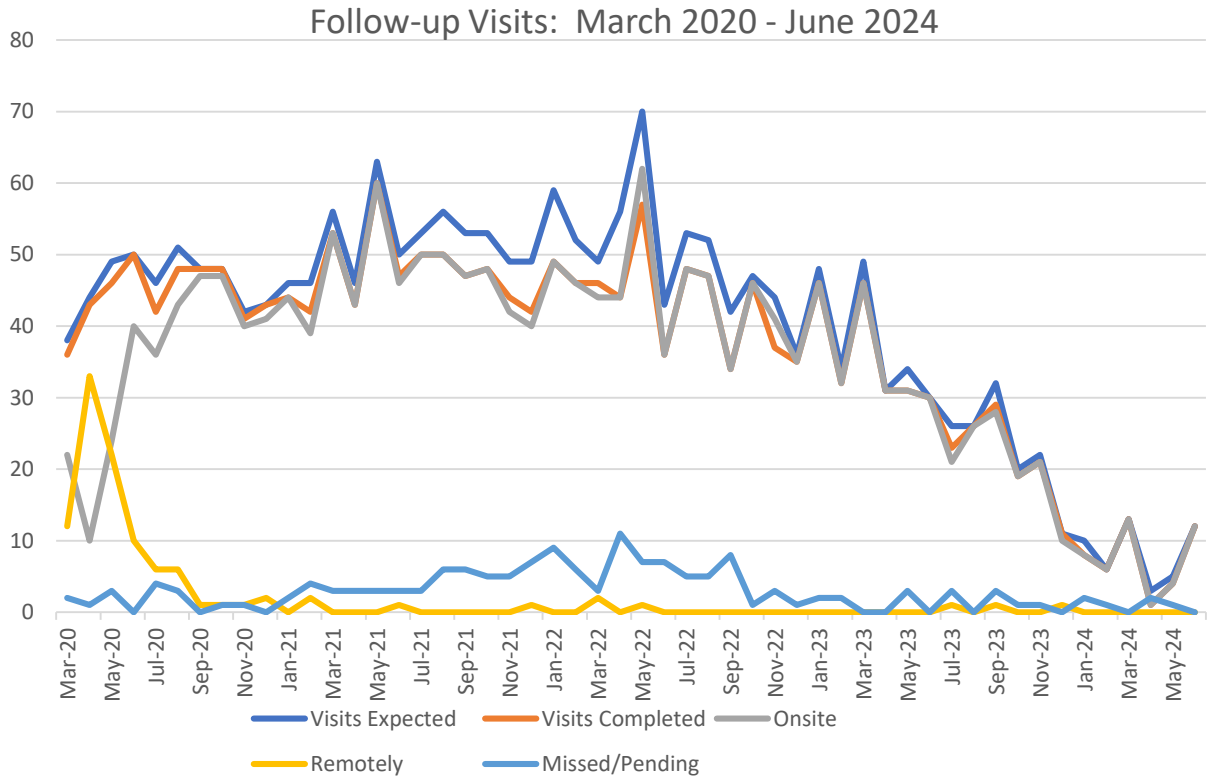
- To find out if low dose treatment for 12 months with oral valacyclovir reduces the chronic pain syndrome called post herpetic neuralgia (PHN) compared to placebo at 12 and 18 months in patients with HZO

Baseline Characteristics at Enrollment

Prescott, Cohen, Hochman et al. *Cornea* 2024 Feb 27 online (2024; 00:1-8)

- 50% of randomized participants were female
- Both sexes represented in each of the 4 groups (strata)
- 87% of participants were White
- 5% of participants were Hispanic or Latino
- Median age at randomization: 60 years
- 91% had received acute recommended antiviral treatment
- 79% of participants did not receive zoster vaccine prior to enrollment

Follow-up Visits: March 2020 – June 2024



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ZEDS
Zoster Eye Disease Study

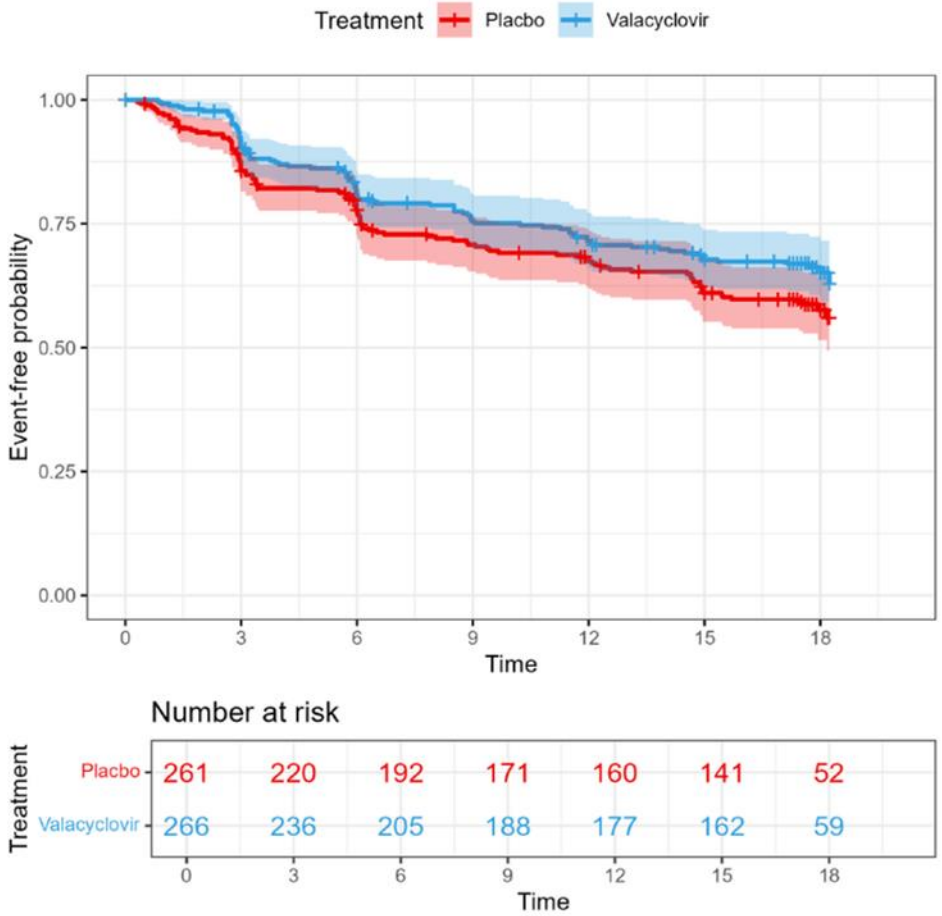
RESULTS

Flow of Participants Through Study

- Screened for eligibility 651
- Excluded 124
- Randomized **527**
  - Valacyclovir 266
  - Placebo 261
    - *All received assigned study med and included in analysis*
- Follow-up
  - Withdrawn from study **67**
    - Valacyclovir 29
    - Placebo 38
  - Stopped study med 79
    - Valacyclovir 35
    - Placebo 44
      - *No study medication related serious adverse events*
- Completed study (527-67) **460**

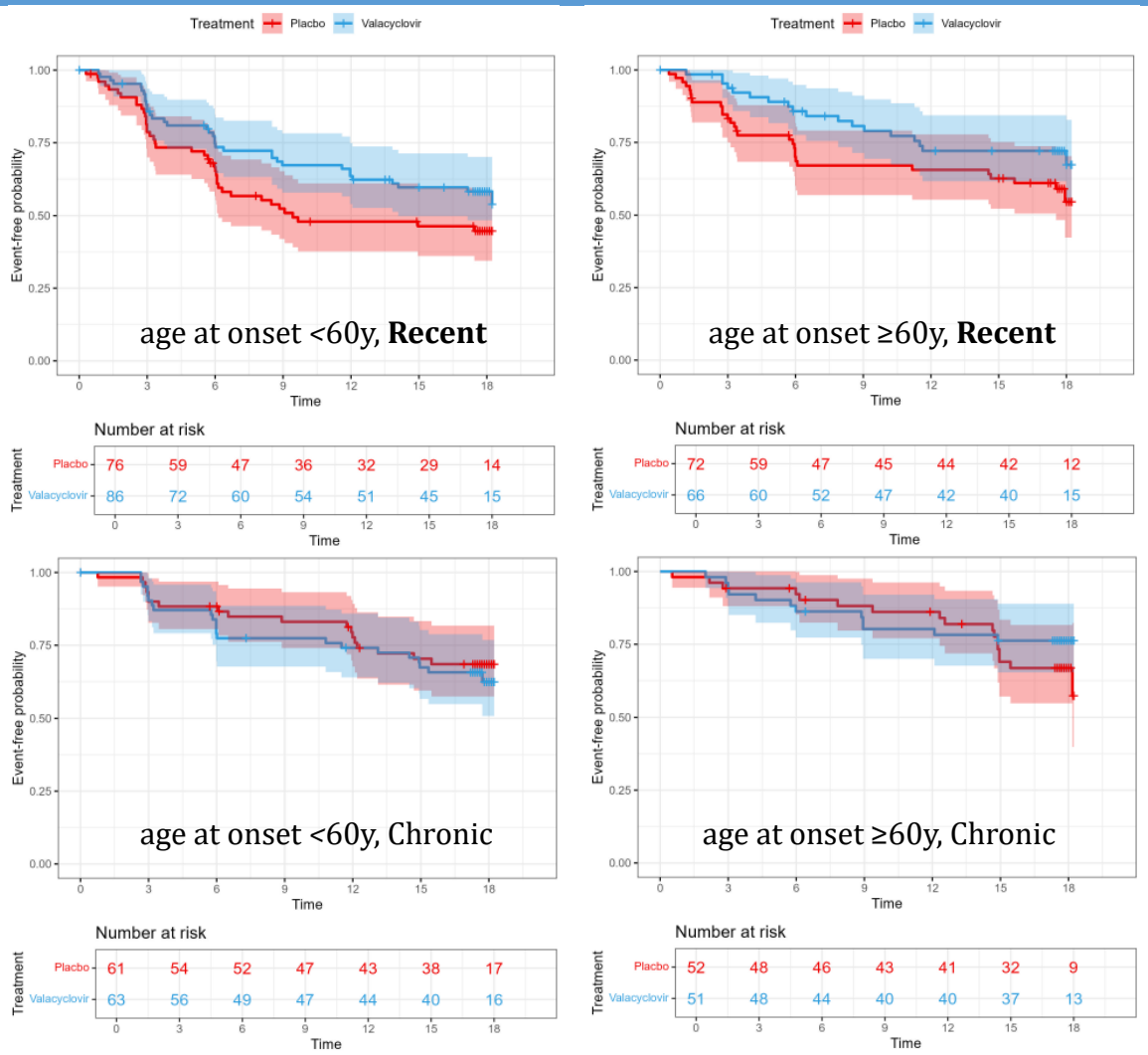
Primary Endpoint Analysis: Kaplan Meier by Treatment Overall

- Graph shows likelihood of **not** having new or worsening disease over time
- No significant treatment benefit in reducing new/worsening disease at *primary endpoint* of 12 months of treatment, but **significant benefit for *secondary endpoint* at 18 months (p=0.04)**



Shading indicate 95% confidence intervals

Primary Endpoint Analysis: Kaplan Meier Curves by Treatment Within Group (Strata)



Statistical Analysis of Benefit in Each of Four Groups (Strata)

- Suggestion of benefit in pre-specified analysis
  - At 12 months <60, Recent onset: p=0.06 [HR: 0.63]
  - At 18 Months <60, Recent onset: p=0.08 [HR: 0.67]

  - Comments
    - HR is hazard ratio: HR: 0.63 means 37% reduction
    - P< 0.05 statistically significant
      - But does not measure importance of result, need to focus on clinical meaningfulness

Valacyclovir Treatment Benefit for Recent Onset HZO (Enrolled within 6 months)

- Analysis by combining recent onset strata (*not pre-specified*) showed significant reduction in endpoints in recent onset HZO
  - 12 months HR=0.65, p = 0.03
  - 18 months HR=0.64, p = 0.02

- Comments:
  - Consider clinically meaningful in guiding care, although not pre-specified in the statistical analysis plan

Significant Valacyclovir Treatment Benefit in Reducing Multiple Flare-ups

- **Participants randomized to Valacyclovir had a significantly lower likelihood of experiencing subsequent disease flare-ups compared to those on placebo**
  - At 12 months: HR: 0.70, p = 0.02
  - At 18 months: HR: 0.72, p = 0.02

ZEDS Guidance for Evidence-based Clinical Practice

- Evidence supports suppressive valacyclovir treatment 1000 mg daily for one year to reduce new or worsening keratitis or iritis in immunocompetent, non pregnant adults with good renal function
  - Pre-specified analysis of primary endpoint did not show overall benefit at 12 months, but did at 18 months (secondary endpoint)

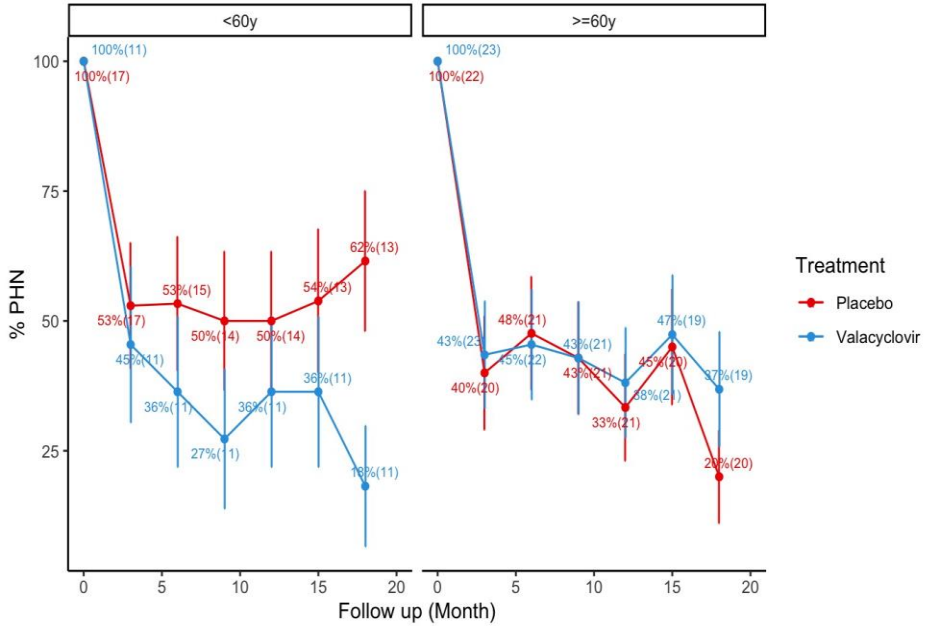
- Evidence supports suppressive valacyclovir treatment to reduce multiple episodes of keratitis or iritis

Second Aim: Postherpetic Neuralgia (PHN)

- Zoster Brief Pain Inventory (ZBPI) score of worst pain in last 24 hours of 3/10 or more occurring 3 or more months after HZO onset was used to define PHN
- The effect of valacyclovir treatment on medication usage for pain was also analyzed
- At enrollment 14% of participants had PHN
- PHN was significantly more common in participants with HZO onset age 60 or older (20%, p=0.007)
  - But PHN also occurred in younger participants (9%)

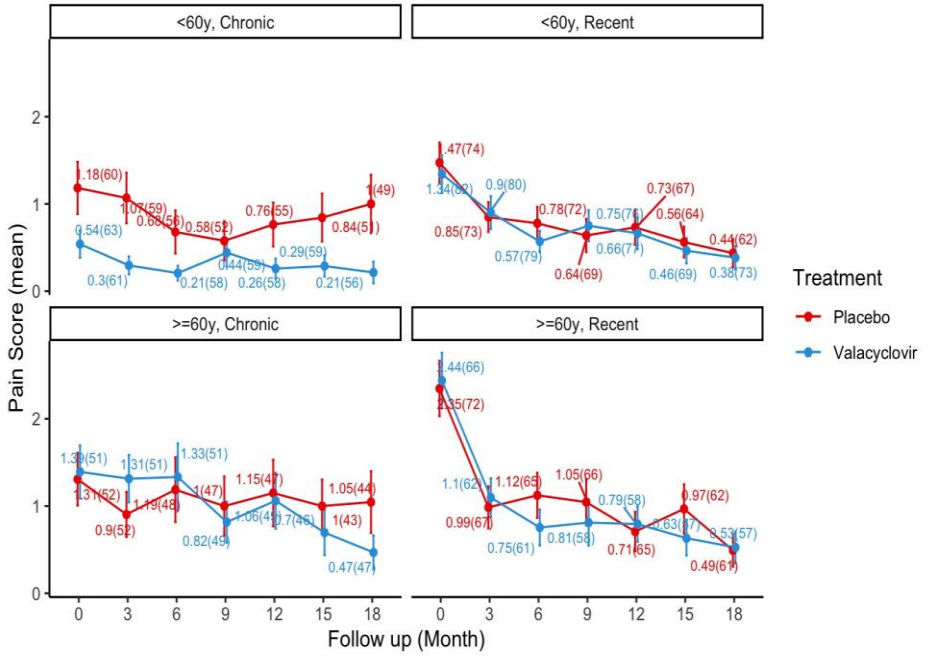
Participants with PHN at Enrollment

- Prevalence not reduced overall
- Participants <60 years at HZO onset on valacyclovir had a significantly lower prevalence of PHN at 18 months (p=0.05)
  - Graph shows percent of participants with PHN over time
  - Combined group analysis by age, not pre-specified



Pain Scores

- Graphs show pain scores over time for each group
- Participants in the <60 years onset, chronic stratum on valacyclovir had significantly lower pain scores at 12 and 18 months (p=0.045, p=0.020)
- Participants on valacyclovir in the ≥60y, chronic stratum had a suggestion of greater decrease in pain at 18 months (p=0.07)



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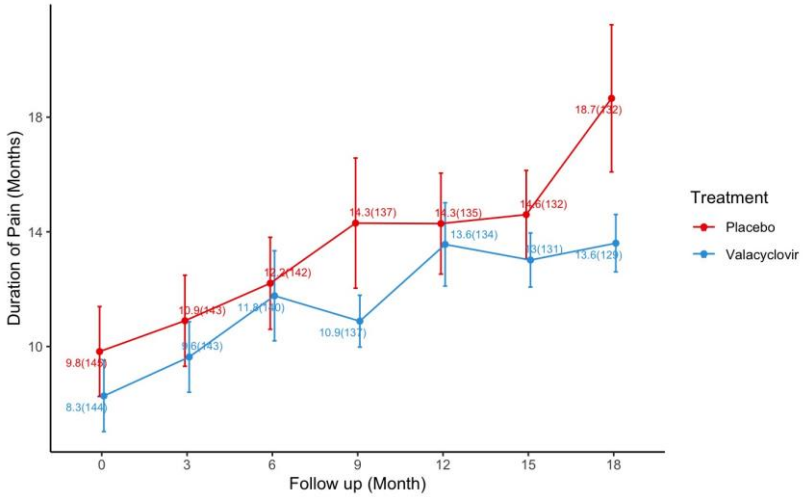
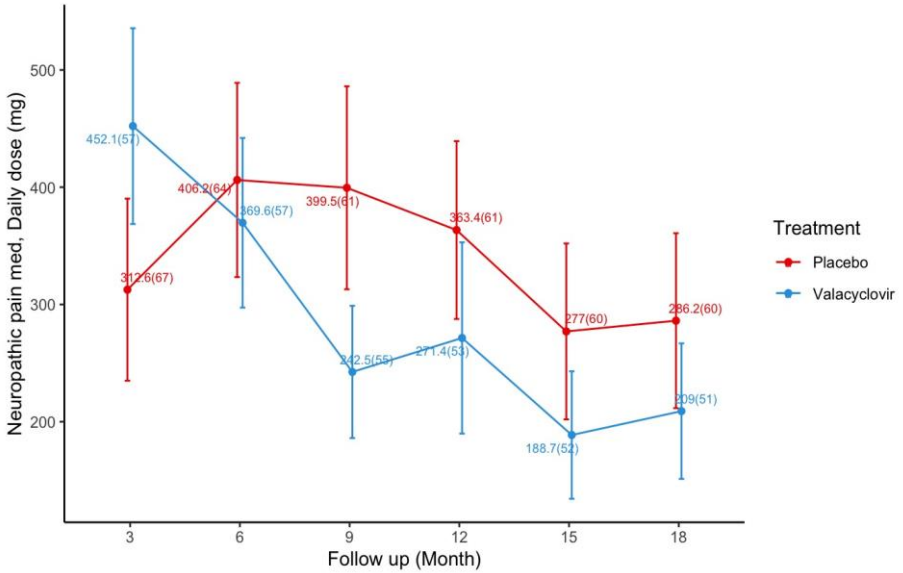
Pain Duration

- Graph shows duration of pain over time
- Among all participants there was a significant decrease in pain duration for those on valacyclovir compared to placebo at 18 months (p=0.05)



Change in Dose of Neuropathic Pain Medications

- Graph shows dosage of pain medicine over time
- There was a statistically significant reduction in the dose of neuropathic medications at 12 and 18 months, (p=0.006 and p=0.012, respectively) for participants on valacyclovir
- This was a pre-specified analysis with significant benefit across strata at both times!



ZEDS Guidance for Evidence-based Treatment of PHN/Pain

- Recommend 1 year of suppressive valacyclovir in HZO patients
  - HZO Onset < 60 years, chronic stratum
    - Significantly lower pain scores at 12 (p=0.05), 18 months (p=0.02)
  - HZO Overall
    - Significant decrease pain duration at 18 months (p=0.05)

- Why is benefit greater at 18 months?
  - Speculation: takes injured nerves time to heal??

ZEDS Guidance for Evidence-based Treatment of PHN

- Recommend one year of suppressive valacyclovir to significantly reduce dose of neuropathic pain meds at 12 and 18 months (p=0.006, p=0.012)

- Comments
  - Valacyclovir safe and better tolerated than neuropathic pain meds
  - Treatment benefit for PHN due to zoster in other locations merits study

Thank you!

- ZEDS achieved aims of developing high quality guidelines for use of low dose valacyclovir to improve outcomes in HZO and PHN/pain that will benefit many patients.
- Please contact your study investigator if you have any questions or would like more information.
- Special appreciation to our study participants who volunteered and made the ZEDS successful!

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Thank you

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