# Enhanced pharmacokinetics profile of pegunigalsidase alfa (PRX-102) supports once-monthly 2mg/kg dosing for the treatment of Fabry disease

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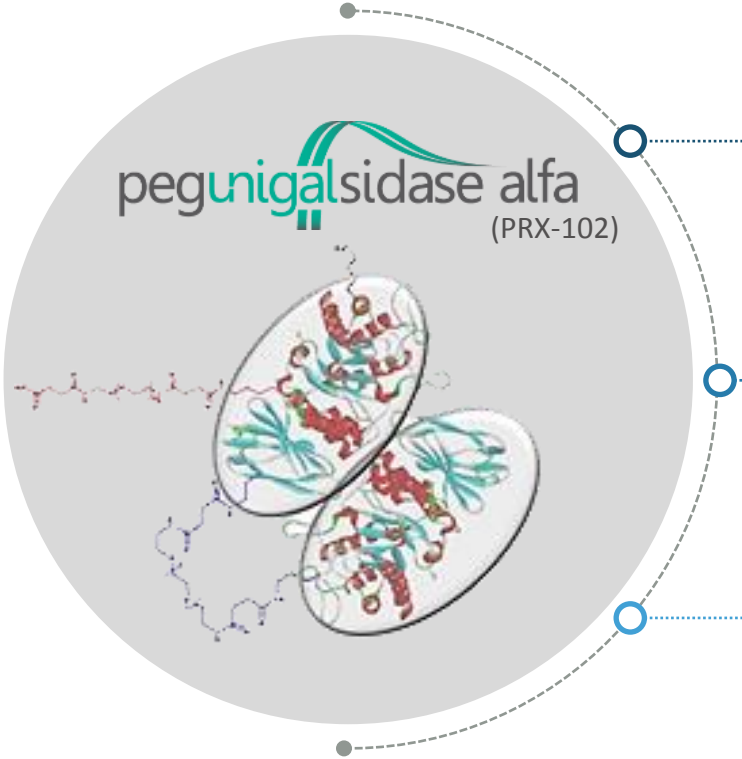
# Disclosures Information
# David G. Warnock

- DG Warnock has active consulting arrangements with Genzyme Corporation, Idorsia, Protalix and Reata
- These activities have been fully disclosed and are managed under a Memorandum of Understanding with the Conflict of Interest Resolution Board of the University of Alabama at Birmingham
- As a US physician, my treatment experience is limited to Fabrazyme at 1 mg/kg IV given every other week

# **pegunigalsidase alfa:** a stabilized α-Gal-A enzyme – Offers an opportunity for prolonged intervals between infusions



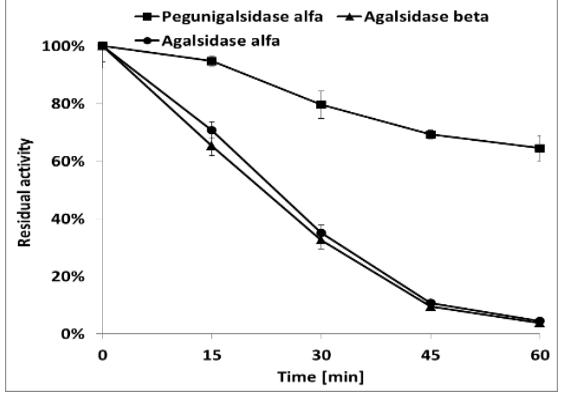

PEGylated covalently-linked homodimer composed of two subunits produced in plant cells

Subunits linked together through the 2000Da PEG cross-linker resulting in 114 kDa enzyme

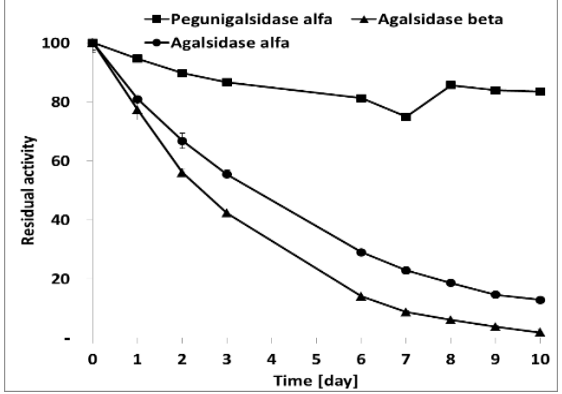
Contains additional PEG moieties bound to only one subunit through a lysine residue

# Extended Stability in Biological Matrices *in-vitro*
## Compared to the Other ERTs

**Stability in human plasma at 37°C (pH=7.4)**




**Stability in lysosomal-like conditions (pH=4.6)**



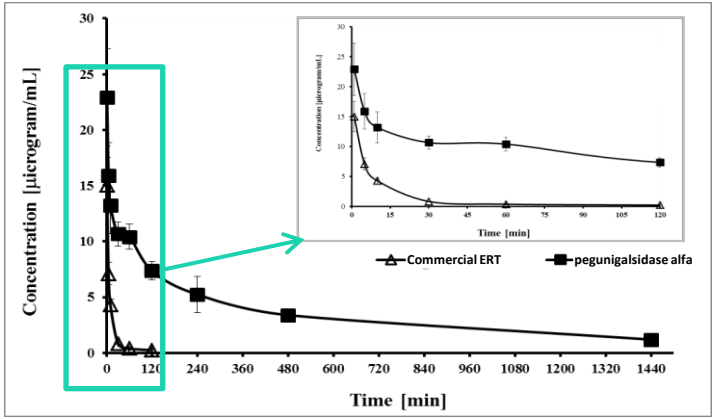

*In-vitro* studies indicated that the pegunigalsidase alfa has improved stability in biological matrices, which could improve pharmacokinetics and pharmacodynamics properties.

Extended half-life suggests the potential for an alternative treatment regimen - every 4 weeks.

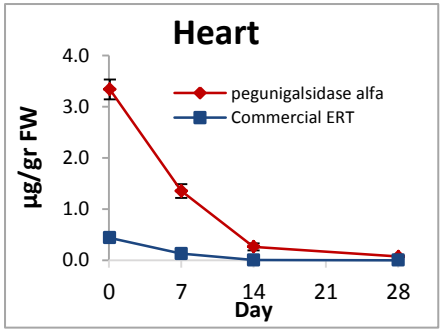
# Extended Pharmacokinetics & Prolonged Activity in Target Organs of Fabry Mice

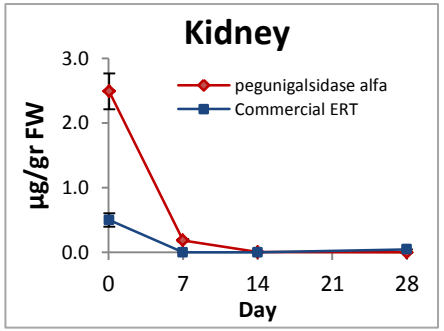
## *In-Vivo* - Further support for the alternative treatment regimen – once every 4 weeks

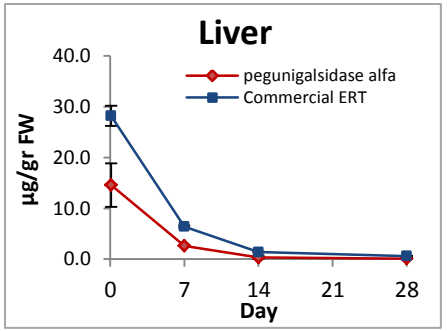
**Extended Pharmacokinetics in Fabry mice model**
(quantified by activity assay)




- **Increased delivery of the active enzyme to the target organs**
- **Reduced clearance by the liver**
  (quantified by activity assay)



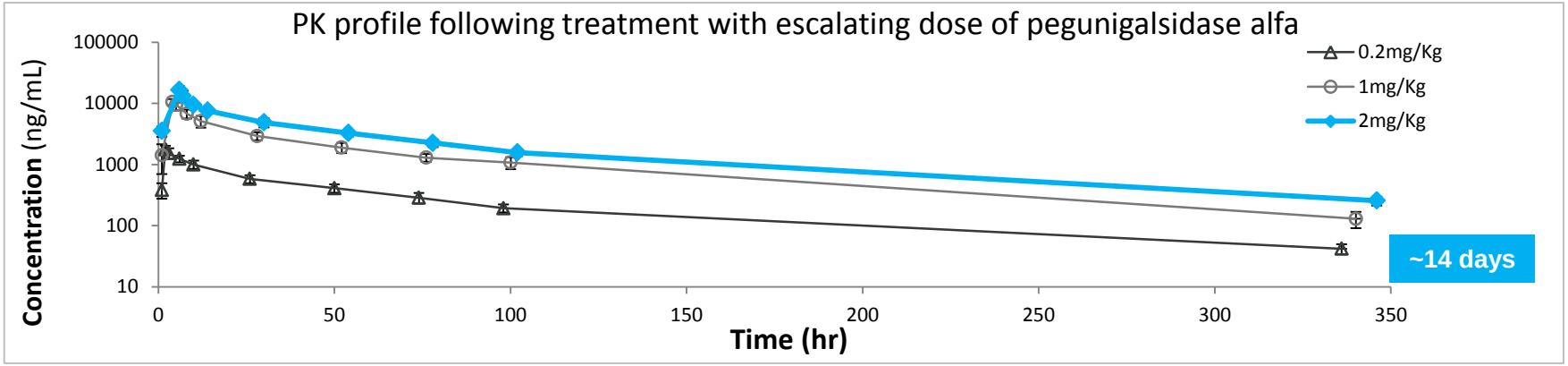



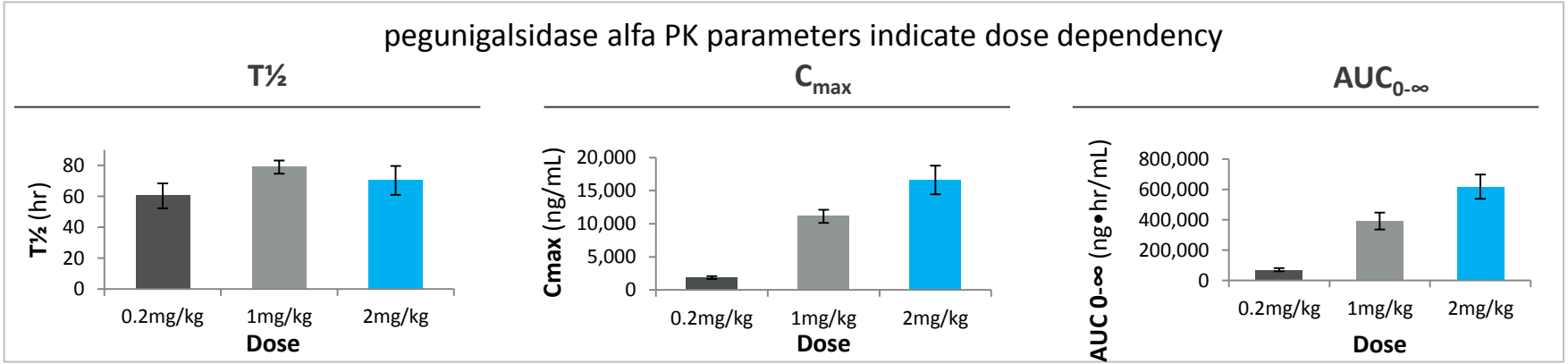




µg/gr FW = amount of enzyme [µg] per gr of tissue fresh weight [FW]

# Pharmacokinetics (PK) in Fabry Disease Patients

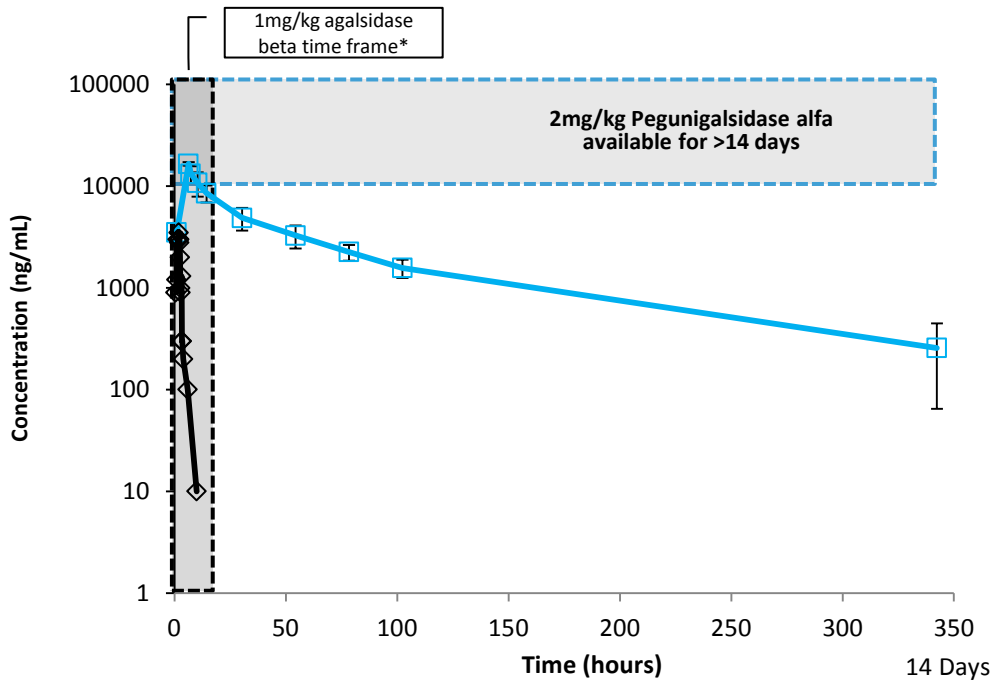
## Increased Stability and Extended Half Life



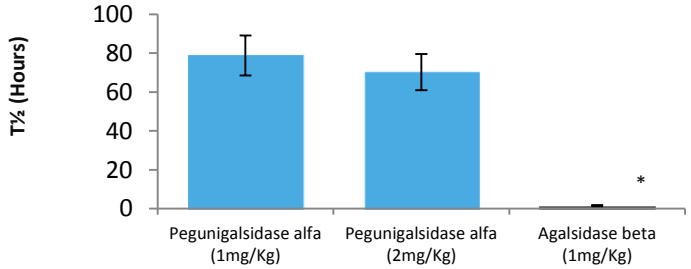



# Substantially Greater Enzyme Exposure Than Current ERTs*

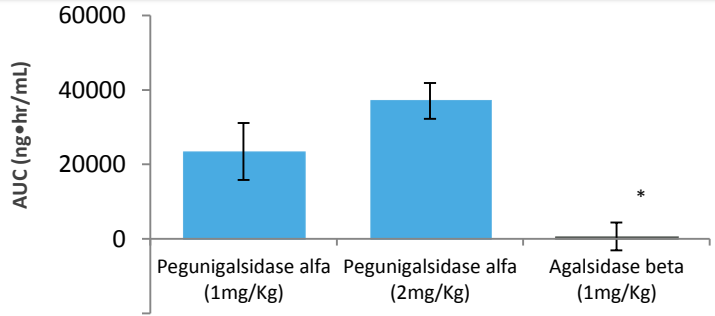
## Plasma drug concentration vs. time




## T½: of ~ 80 hours ; ~40 fold longer than current ERTs



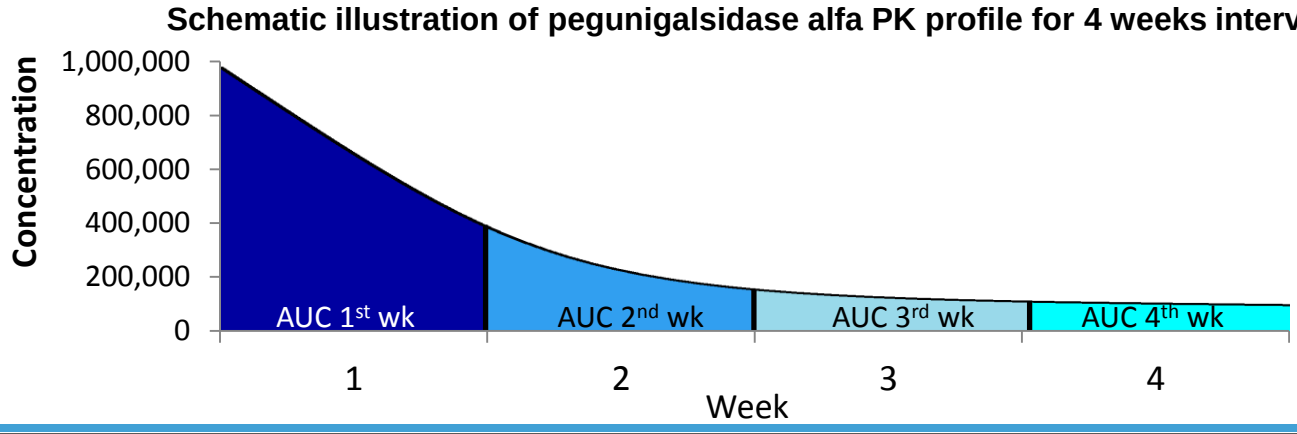

## AUC (0-∞): ~60 fold higher than current ERTs



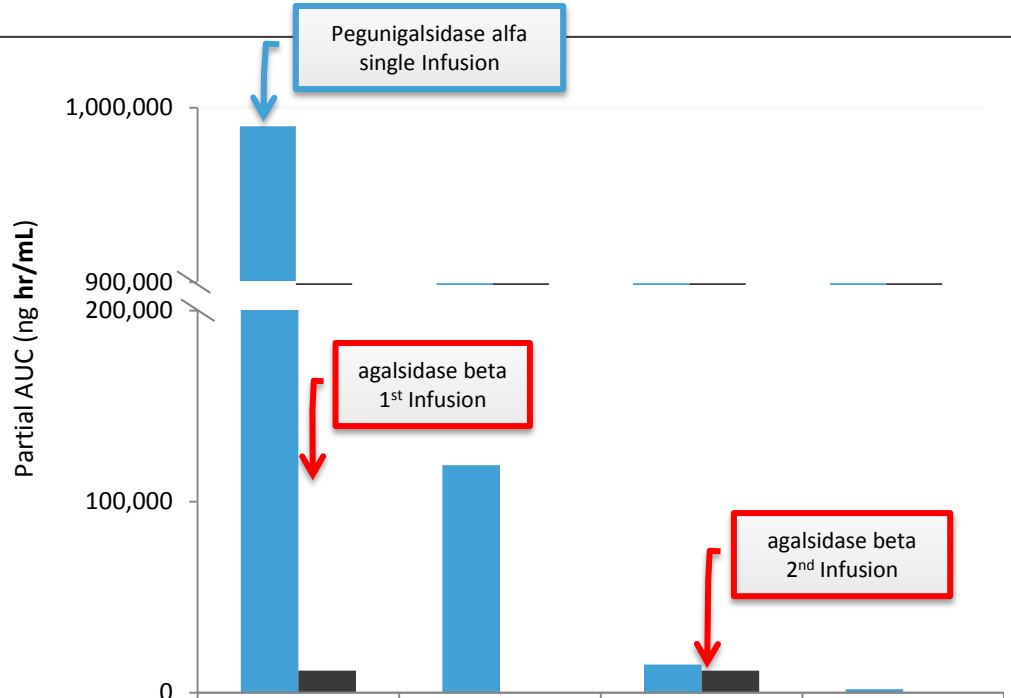

*agalsidase beta – USPI ; AUC units: ng•hr/mL; 1ng•hr/mL = 0.06 µg•min/mL

# Analysis Process and Projection Modeling Approach

- PK data obtained from the Phase I/II study
- Information on the PK characteristics of agalsidase beta (Fabrazyme®) is available in the package insert (agalsidase beta USPI) and in Eng et al, 2001
- Projection modeling was done using  Phoenix WinNonlin Software
- Weekly Partial AUC and average concentration ($C_{ave}$) calculations enabled the comparison and estimation of the drug availability on weeks 1, 2, 3 and 4 of pegunigalsidase alfa and compared it to agalsidase beta every 2 weeks



# Comparative PK Projection Modeling




| | 1 | 2 | 3 | 4 |
|---|---|---|---|---|
| pegunigalsidase , 2 mg/kg | 989,406 | 119,065 | 14,637 | 1,799 |
| agalsidase beta, 1 mg/kg* | 11,600 | 0 | 11,600 | 0 |

Partial AUC = Area Under the Curve calculated per week

**Greater AUC in a single IV infusion of 2 mg/kg pegunigalsidase alfa, compared to 2 infusions of 1 mg/kg agalsidase beta over a 4 week time frame:**

- **Measurable levels of pegunigalsidase alfa in the 3rd and 4th week after single infusion.**
- **3rd week after a single 2mg/kg pegunigalsidase alfa IV- has the same order of magnitude as agalsidase beta after the 2nd infusion.**
- **4th week after 2mg/kg pegunigalsidase alfa IV – higher levels than the negligible agalsidase beta levels in the 2nd week after 2nd infusion.**

*based on agalsidase beta - USPI

# Results leading to the design of a clinical study of monthly treatment

- **An enhanced PK profile of 2mg/kg pegunigalsidase alfa was observed in Phase I/II:**
  - **Half-life ($t_{½}$)** is approximately 80 hr Vs. ~2 hr of the commercially available ERTs
  - **$C_{max}$** values are about **10-fold** higher than those published for Fabrazyme® (Fabrazyme® USPI, 2010)
  - **$AUC_{0-\infty}$** values are about **60-fold** greater than those published for Fabrazyme®
- **Comparative PK projection modeling estimating the weekly partial AUC and average concentration ($C_{ave}$) indicate that:**
  - For therapeutic coverage, a patient could get a single 2mg/kg pegunigalsidase alfa infusion vs. 2 infusions of the commercial ERTs per month
    - 3rd and 4th week after infusion– a measurable levels of pegunigalsidase alfa
    - 3rd week - the same order of magnitude as Fabrazyme® in the 1st week after the 2nd infusion
    - 3rd and 4th week - **higher** than the negligible Fabrazyme® levels in the 2nd week after each infusion.
- **The results of the PK projection modelling, suggest that dosing with pegunigalsidase alfa 2.0 mg/kg every 4 weeks would be beneficial in patients with Fabry Disease**

# Outline of the On-Going Clinical Study – BRIGHT

## Study Objectives & Design

- Open label switch over study to evaluate the safety and efficacy of **2.0 mg/kg** pegunigalsidase alfa every **4 weeks**
- Patients with Fabry disease currently treated with agalsidase alfa **or** agalsidase beta switched to pegunigalsidase alfa
- Treated with ERT for at least 3 years, and on the same dose (>80% labelled dose/kg) for at least 6 months before the switch to pegunigalsidase alfa.
- **Study Duration:** 12 months treatment on pegunigalsidase alfa 2 mg/kg every 4 weeks
- **30 patients**, 15±3 from each enzyme
- After completion, patients will be offered enrollment in a open label extension study under pegunigalsidase alfa

bright A Fabry clinical study of once-monthly ERT

# Bright Enrolling Sites

| Country | | Investigator | | Investigator Contact info |
|---|---|---|---|---|
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# Summary & Conclusions

- The unique characteristics of pegunigalsidase alfa, as well as the safety and efficacy results from phase I/II and the PK projection modelling, provide the rationale for initiating a phase 3 study that will assess the safety, efficacy and PK of 2 mg/kg pegunigalsidase alfa administered IV every 4 weeks in adult patients with Fabry disease.
- Treating patients every 4 weeks is expected to improve the quality of life and treatment compliance with lower treatment burden while maintaining clinical stability with **half the infusions** compared to currently approved ERT.
- This dose and once-monthly regimen have the potential to result in a comparable efficacy and safety profile with a reduced immunogenicity compared to current ERTs.
- This has the potential to delay the risk of developing disease complications in mild to moderate patients by slowing disease progression.

# Acknowledgements


## Special thanks to:

- **Study site clinical teams**
- **Co-authors: Martha R. Charney[1], Derralynn Hughes[2], Raphael Schiffmann[3], Sari Alon[4], Raul Chertkoff[4], Einat Brill-Almon[4]**

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# Thank You