Alteplase for the Treatment of Acute Ischemic Stroke in Patients with Low NIHSS and Not Clearly-Disabling Deficits: Primary Results of the PRISMS Trial

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On Behalf of the PRISMS Collaborators

Sponsor: Genentech, Inc

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Relevant Disclosures

- **Pooja Khatri, MD, MSc**
  - Alteplase for the Treatment of Acute Ischemic Stroke in Patients with Low NIHSS and Not Clearly-Disabling Deficits: Primary Results of the Prisms Trial

- **Financial Disclosures:**
  - UC Dept of Neurology received funds from Genentech (PRISMS Trial PI), Lumosa (consultation, DSMB), and Neurospring (clinical advisory board) for my research effort
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- **Unlabeled/Unapproved Uses Disclosure:**
  - Alteplase use for strokes with minor deficits

Background

- **Over half of all ischemic strokes present with NIHSS 0-5**

Stroke. 2013;44: 3211-3213;
Stroke. 2009;40:2805-2811.

- **In subset with deficits judged nondisabling, the benefit of alteplase is unclear**
  - Few were enrolled in major RCTs

Trials	Minor Stroke Exclusion Criteria
NINDS Parts 1 & 2	Minor symptoms (including 4 prespecified syndromes)
ECASS I & II	Scandinavian Stroke Scale (SSS) <50
ATLANTIS A &B	NIHSS <4 and normal speech and visual fields
ECASS III	Only minor symptoms
EPITHET	NIHSS <5
IST-3	None (but only if if enrolling physician with personal equipoise regarding benefit)

Stroke. 2015;46:2325-2327

  - Guidelines reflect community equipoise for this subset
    - AHA/ASA Class IIb; Level of Evidence C

Stroke. 2013 Mar;44(3):870-947;
Stroke. 2016 Feb 1;47(2):581-641

Objective of PRISMS Trial

- To evaluate the efficacy and safety of IV alteplase for ischemic stroke patients with **minor deficits (NIHSS 0-5) judged not clearly-disabling at presentation** in a Phase 3b, double-blind, active-controlled, randomized, multicenter trial

  - Operational definition of “not clearly-disabling”

    ✓ Can patient still do basic ADLs and/or return to work?

BASIC ADLs

Bathing/Dressing ‣ Ambulating (walking)

Toileting ‣ Hygiene ‣ Eating

(“BATHE”)

Key Eligibility Criteria

- **Inclusion criteria**
  - Age 18 years or older
- **Exclusion criteria**
  - Pre-stroke disability (modified Rankin Scale 2-6)
  - Other standard contraindications to IV alteplase
    - 2013 AHA/ASA acute ischemic stroke guidelines

Intervention

- **Randomization (1:1)**
  1. IV alteplase (0.9 mg/kg, max 90 mg) with placebo oral aspirin
  2. Oral aspirin (325 mg) with placebo intravenous alteplase (control)

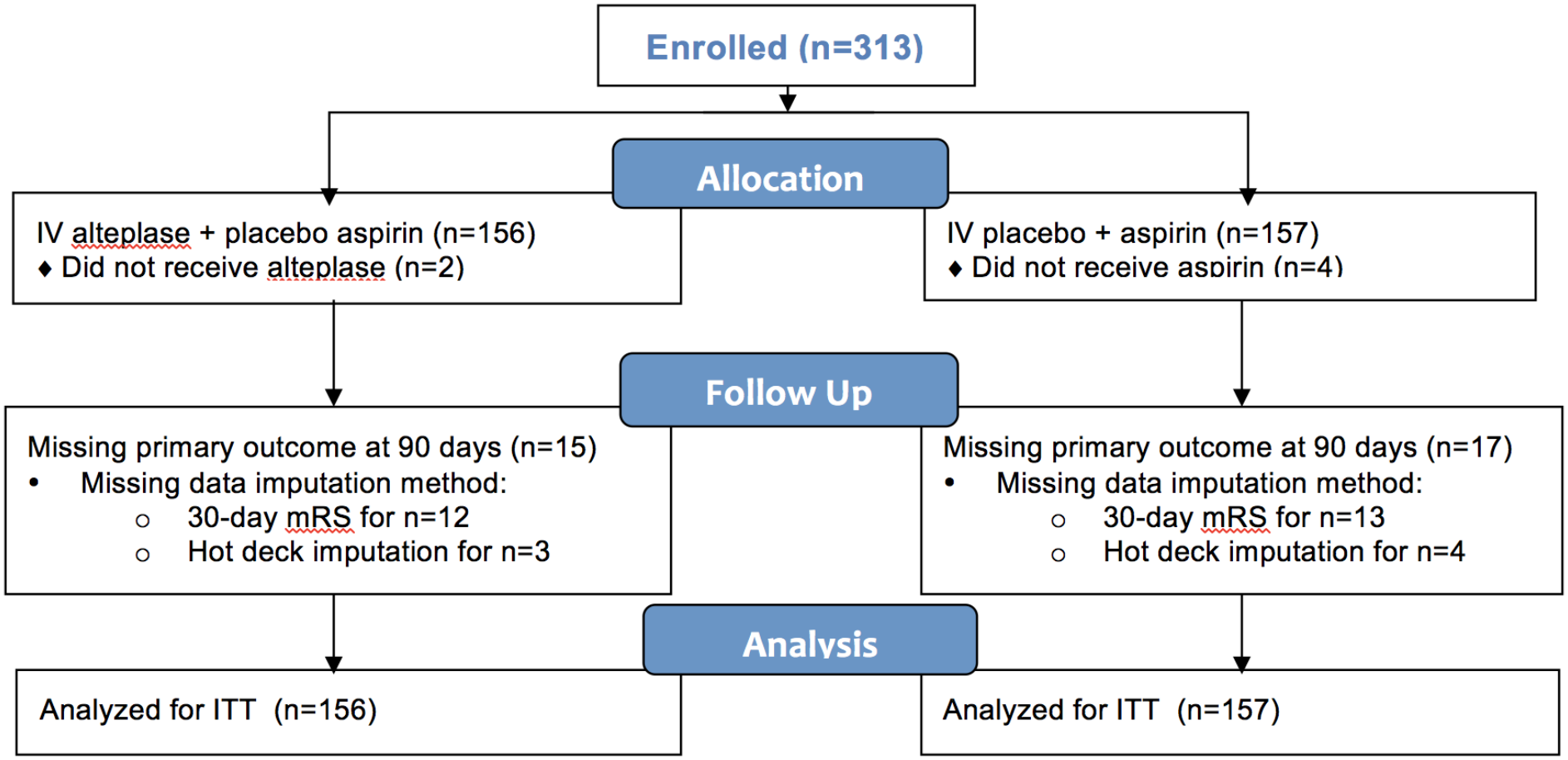
- **IV study drug initiated within 3 hours of last known well**

Study Endpoints

- **Primary endpoint**
  - Functional outcome (mRS 0 or 1) at 90 days
- **Secondary efficacy endpoints**
  - Ordinal mRS (0, 1, 2, 3, 4, 5−6) at day 90
  - Global test (mRS 0−1, NIHSS 0−1, BI ≥95, and GOS=1) at day 90
- **Primary safety endpoint**
  - Symptomatic intracranial hemorrhage (sICH) within 36 hours
    - Any neurological decline attributed to ICH (modified NINDS definition)

Results

- 313 of 948 planned patients were enrolled over 32 months
- Halted early by sponsor – below recruitment targets



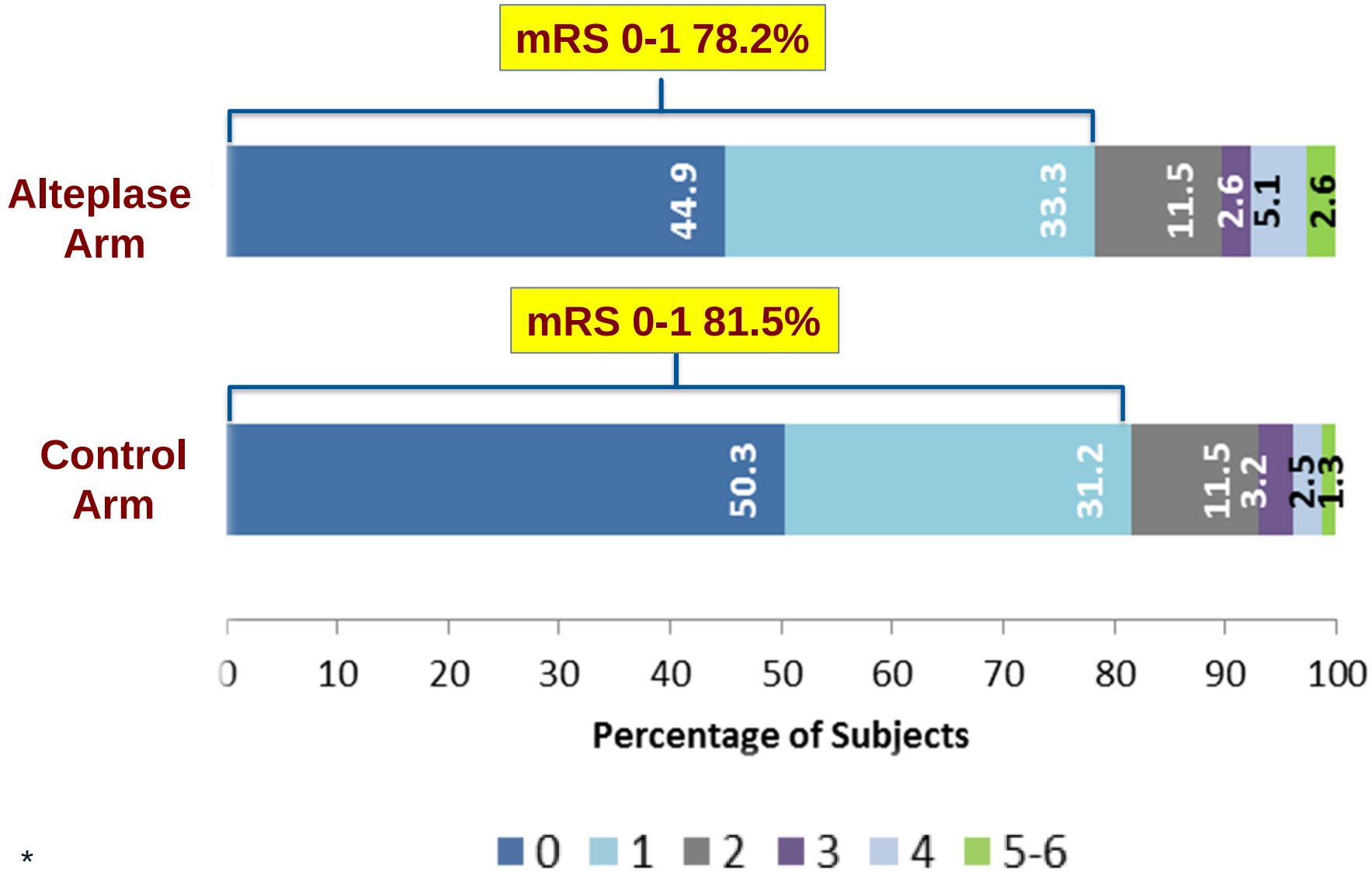
Baseline Patient Characteristics

Characteristic	Alteplase (n = 156)	Control (n = 157)
Age, years, mean (SD)	62 (13.5)	61 (13.05)
Male Sex, n (%)	77 (49.4)	92 (58.6)
Black Race, n (%)	35 (22.4)	27 (17.2)
Hispanic/Latino Ethnicity, n (%)	14 (9.0)	18 (11.5)
Hypertension, n (%)	126 (81.3)	124 (79.0)
Hyperlipidemia, n (%)	114 (73.1)	114 (72.6)
Diabetes Mellitus, n (%)	57 (36.5)	44 (28.0)
Previous Stroke, n (%)	28 (17.9)	24 (15.3)
Atrial Fibrillation, n (%)	23 (14.7)	17 (10.8)
Antiplatelet Agents, n (%)	64 (41.0)	59 (37.6)
Systolic Blood Pressure, mm Hg, mean (SD)	145 (22.3)	149 (18.8)
Baseline ASPECTS Score, median (range)	10 (7, 10)	10 (7, 10)
Time—Onset to IV Bolus, hours, median (IQR)	2.7 (2.2, 2.9)	2.6 (2.1, 2.9)
Time—Onset to Oral Study Drug, hours median (IQR)	2.9 (2.5, 3.1)	2.8 (2.4, 3.1)

Presenting Event Characteristics

Characteristics	Alteplase (n = 156)	Control (n = 157)
Localization of Presenting Deficit		
Right Hemisphere, n (%)	75 (48.1)	67 (42.7)
Left Hemisphere, n (%)	59 (37.8)	62 (39.5)
Unknown, n (%)	19 (12.2)	21 (13.4)
Brain Stem/Cerebellum, n (%)	9 (5.8)	18 (11.5)
Final Diagnosis of Neurovascular Mimic, n (%)	18 (11.7)	22 (14.4)
Ischemic Cerebral Event Etiology, n	138	135
Small Vessel Disease , n (%)	48 (34.8)	52 (38.5)
Undetermined Etiology , n (%)	40 (29.0)	46 (34.1)
Cardioembolism, n (%)	20 (14.5)	17 (12.6)
Large Artery Atherosclerosis, n (%)	20 (14.5)	10 (7.4)
Other Determined Etiology, n (%)	10 (7.2)	10 (7.4)

Distribution of mRS at Day 90



*

Primary Outcome

Primary Outcome	Adjusted Risk Difference* (95% CI)
mRS 0–1 at Day 90, n (%)	-1.10% (−9.44, 7.25)

**Adjusted risk difference is obtained from a linear regression with treatment, age, onset time to treatment, baseline NIHSS, and quadratic terms for age, baseline NIHSS as covariates.*

*

Prespecified Secondary/Exploratory Analyses of Efficacy

	Alteplase (n=156)	Control (n=157)	Effect Estimate – Risk Difference or Odds Ratio (95% CI)
SECONDARY ENDPOINTS (90 DAYS)			
mRS 0-1, unadjusted	122 (78.2%)	128 (81.5%)	-3.3% (-12.2%, 5.6%)
Global Test			0.86 (0.53, 1.39)
EXPLORATORY ENDPOINTS (90 DAYS)			
mRS 0	70 (44.9)	79 (50.3)	-3.6% (-14.2%, 7.1%)
NIHSS 0-1	108 (85.7)	98 (81.7)	1.30 (0.65, 2.59)
BI 95-100	107 (79.3)	118 (88.7)	0.53 (0.26, 1.06)
GOS 1	110 (81.5)	113 (85.6)	0.80 (0.41, 1.59)
Ambulatory Performance (comfortable walking speed, meters per second)	0.95 (0.34)	0.98 (0.44)	-0.03 (-0.13, 0.08)
EQ-5D, mean (SD)	0.81 (0.21)	0.83 (0.20)	-0.02 (-0.07, 0.03)
SIS-16, mean (SD)	85.1 (21.0)	86.3 (21.4)	-1.1 (-6.2, 4.0)

Additional Exploratory Analyses for the Primary Outcome

	Alteplase (n=156)	Control (n=157)	Effect Estimate – Risk Difference or Odds Ratio (95% CI)
Acute Cerebral Ischemia Cases Only (mimics excluded)	107 (77.5)	109 (80.7)	-4.1 (-12.6, 4.5)
Propensity Score-Adjusted Model			-2.4% (-11.2%, 6.4%)
Logistic Regression Model			0.95 (0.53, 1.71)
Repeated Measures Model			0.86 (0.51, 1.44)

Primary Safety Outcome (As Treated)

	Alteplase (n=154)	Control (n=153)	Risk Difference (95% CI)
sICH within 36 hours	5 (3.2)	0 (0.0)	3.3% (0.8%, 7.4%)

Other Safety Outcomes (As Treated)

	Alteplase (n=154)	Control (n=153)	Risk Difference (95% CI)
Any ICH within 36 hours (central reader)	11 (7.1)	5 (3.3)	3.9% (-1.2%, 9.5%)
Radiological Subtype of ICH*			
HI-1	2	3	
HI-2	2	1	
PH-1	1	0	
PH-2	4	0	
Remote PH-1	2	0	
IVH	2*	0	
SAH	3*	1	
Mortality	1 (0.6)**	0	

*These patients have more than one subtype
**Patient death unrelated to study drug (volvulus)

Likelihood of Alteplase Benefit (Post Hoc Bayesian Analysis)

- For clinical interpretation and future trial planning purposes
- Using PRISMS unadjusted outcome proportions added to an uninformative prior

Posterior probability of alteplase benefit

Any benefit = 23%

>6% absolute benefit = 1.9%

95% credible interval of -12.2% to 5.5%

Limitations

- Most important – early termination
  - Low power / precision
- Potential for selective recruitment
  - Intensive efforts to facilitate uniform application of enrollment criteria
  - Still applicable to the patients similar to the final enrolled population
  - Broad cohort with both small and large vessel occlusions
- Rate of missing day-90 outcomes was relatively high
  - However day-30 mRS is known to permit robust imputation

Other Considerations

- First randomized trial evaluating alteplase in this population
- While underpowered, nearly all point estimates (primary, secondary, or exploratory) were unfavorable
- Better 90-day outcome in controls than predicted
  - 81% observed vs ~70% from prior literature
- Increased sICH without an associated increase in mortality

Conclusions

- Among patients with low NIHSS and not clearly-disabling deficits, alteplase may not provide benefit and increases the risk of symptomatic intracranial hemorrhage.
- While early trial termination precludes definitive conclusions, the benefits of alteplase are not likely to extend to those without clearly-disabling deficits at presentation.
- These findings should **not** be extrapolated to patients with NIHSS 0 to 5 and clearly-disabling deficits.

Acknowledgements (1)

ENROLLING SITES		
Investigator	**Institution Name**	**# Enrolled**
Kleindorfer, Dawn	University of Cincinnati	25
Devlin, Thomas	Chattanooga Center for Neurologic Research	24
Sawyer, Robert	Buffalo General Medical Center	22
Starr, Matthew	University of Pittsburgh Cancer Institute	15
Mejilla, Jennifer	Riverside Methodist Hospital	13
Sethi, Pramodkumar	Moses H Cone Memorial Hospital	10
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McIntosh, Gerald	Poudre Valley Health System	7
Tansy, Aaron	Icahn School of Medicine at Mount Sinai	7

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ENROLLING SITES CONTINUED		
Investigator	**Institution Name**	**# Enrolled**
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Modir, Royya	UCSD	4
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Uchino, Ken	Cleveland Clinic	4
Starkman, Sid	UCLA	4

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Azhar, Salman	NYU Lutheran Medical Center	2
Lyerly, Michael	University of Alabama at Birmingham	2
Schrock, Jon	Case Western Reserve University	2
Song, Shlee	Cedars Sinai Medical Center	2
Levine, Steven	SUNY Downstate Medical Center	2
Franz, Douglas	Banner - University Med Ctr Phoenix	2
Song, Sarah	Rush University Medical Center	2
Alhatou, Mohammed	The Neurology And Pain Clinic	1
Felberg, Robert	Overlook Hospital	1
Kabbani, Mouhammed	Gunderson Health System	1
Lee, Jin-Moo	Washington University	1
Singh, Niranjan	University of Missouri	1
Zaidi, Syed	University of Toledo Medical Center	1

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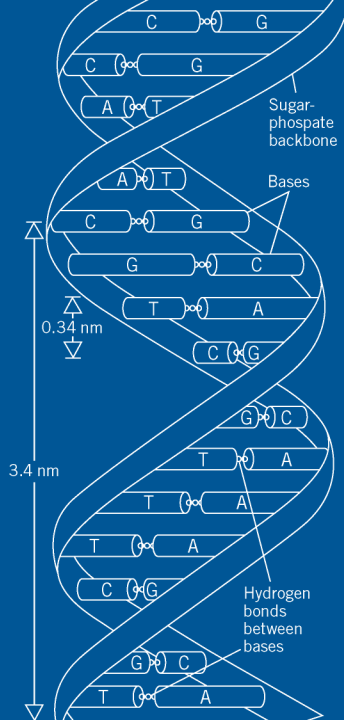
  - *Independent Data Monitoring Committee (iDMC)*: Karen Johnston (Chair), Bill Barsan, Howard Rowley

- **Enrolled Patients and their Families**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THANK YOU