ACC.16

65th Annual Scientific Session & Expo

Short and Long Term Effects of Benznidazole, Posaconazole, Monotherapy and their Combination in Eliminating Parasites in Asymptomatic T. cruzi Carriers: **St**udy of use of **O**ral **P**osaconazole on the Treatment of asymptomatic chronic **CHAGAS** disease (STOP-CHAGAS)

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AT THE INTERSECTION OF SCIENCE & CHANGE

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Short and Long Term Effects of Benznidazole, Posaconazole, Monotherapy and their Combination in Eliminating Parasites in Asymptomatic T. cruzi Carriers:

Study of use of Oral Posaconazole on the Treatment of asymptomatic chronic CHAGAS disease (STOP-CHAGAS)

Carlos A. Morillo, Hetty Waskin, Sergio Sosa-Estani, Maria del Carmen Bangher, Carlos Cuneo, Rodolfo Milesi, Marcelo Mallagray, Werner Apt, Juan Beloscar, Joaquim Gascon, Israel Molina, Luis E. Echeverria, Hugo Colombo, Jose Antonio Perez-Molina, Fernando Wyss, Brandi Meeks, Laura Bonilla, Peggy Gao, Bo Wei, Michael McCarthy, MD, and Salim Yusuf, on behalf of the STOP-CHAGAS Investigators

Disclosures

- STOP-CHAGAS was funded by Merck Sharpe & Dohme
- Study conducted and data base managed and analyzed by the Population Health Research Institute-HHSC, McMaster University, Hamilton, ON, Canada

Rationale

- Chagas disease is due to infection with *T. cruzi* and is among the largest tropical disease burden in the western hemisphere.
- Between 5.7 to 9.4 million people are chronically infected with T. cruzi and the vast majority are in the indeterminate form of the disease (i.e. no evidence of cardiac involvement).
- 17 million Latin American immigrants in 2007, 340,000 of whom were potentially infected by T. cruzi, and approximately 65,000 may develop symptomatic CD, in the U.S.A.

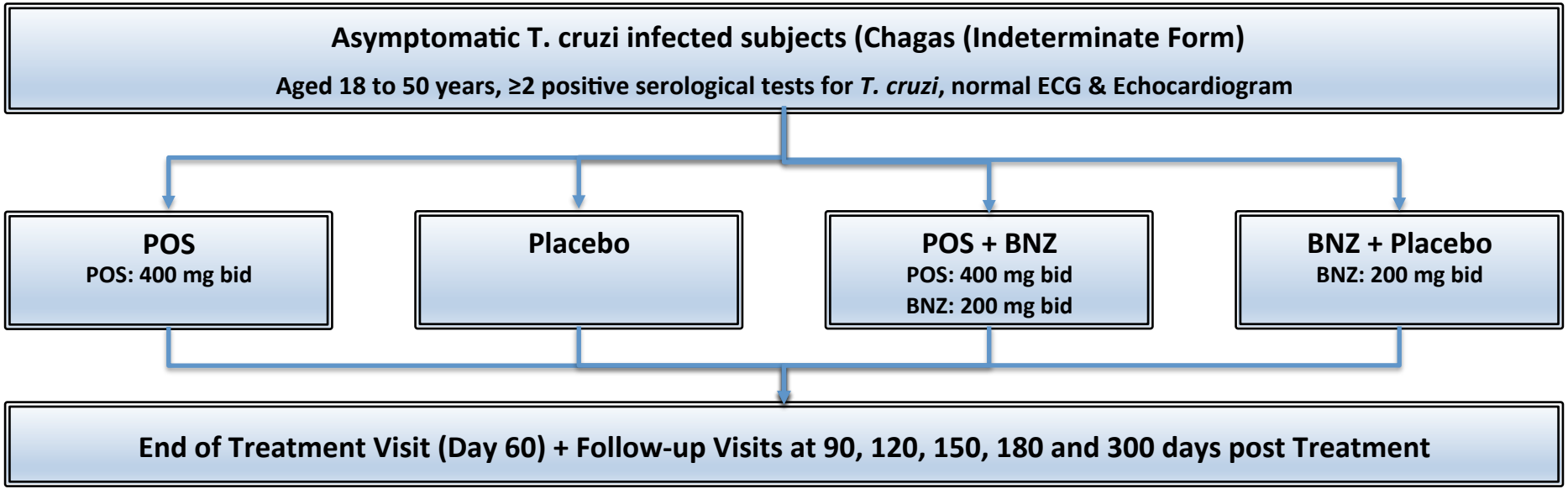
Rationale

- Available treatment include Benznidazole (BNZ) & Nifurtimox but cure rates in chronically infected subjects in the indeterminate stage range between 10-50%.
- Etiologic treatment in T. cruzi infected adults over the age of 18 years remains controversial.
- Posaconazole (POS) has demonstrated experimental and clinical trypanocidal activity. However, a recent trial demonstrated high rates of treatment failure with POS monotherapy.

Objectives

- To evaluate the efficacy of POS compared to Placebo and either BNZ monotherapy or combined with POS as determined by the proportion of negative real time polymerase chain reaction (RT-PCR) after 180 days.
- To evaluate the efficacy and safety of POS vs. Placebo or BNZ, and BNZ+POS at 30, 60, 90, 180 and 360 days.

Study Design



Primary Outcome: proportion with a successful response (conversion RT-PCR) for POS vs placebo and each active arm of either monotherapy or combined therapy of BNZ or POS in reducing parasitemia by determining treatment response as measured by RT- PCR at day 180.

Secondary Outcomes: proportion with a successful response (conversion RT-PCR) for POS vs placebo and each active arm of either monotherapy or combined therapy of BNZ or POS in reducing T. cruzi DNA detection by determining treatment response as measured by RT- PCR at 360 days. Safety monotherapy & combination therapy.

Study Procedures

- 60 day treatment period with follow-up to Day 360
- Adverse events, ECG, liver function tests during treatment period
- Blood samples for RT-PCR to detect *T. Cruzi* DNA & 30, 60, 90, 120, 150,180, & 360 days
- Blood samples for POS pharmacokintetics

Study Treatments

1: POS	Posaconazole 400 mg (10 mL) BID
2: PLA	Posaconazole-placebo 10 mL BID
3: BNZ + POS	Benznidazole 200 mg BID + Posaconazole 400 mg BID
4: BNZ + PLA	Benznidazole 200 mg BID + Posaconazole-placebo 10 mL BID

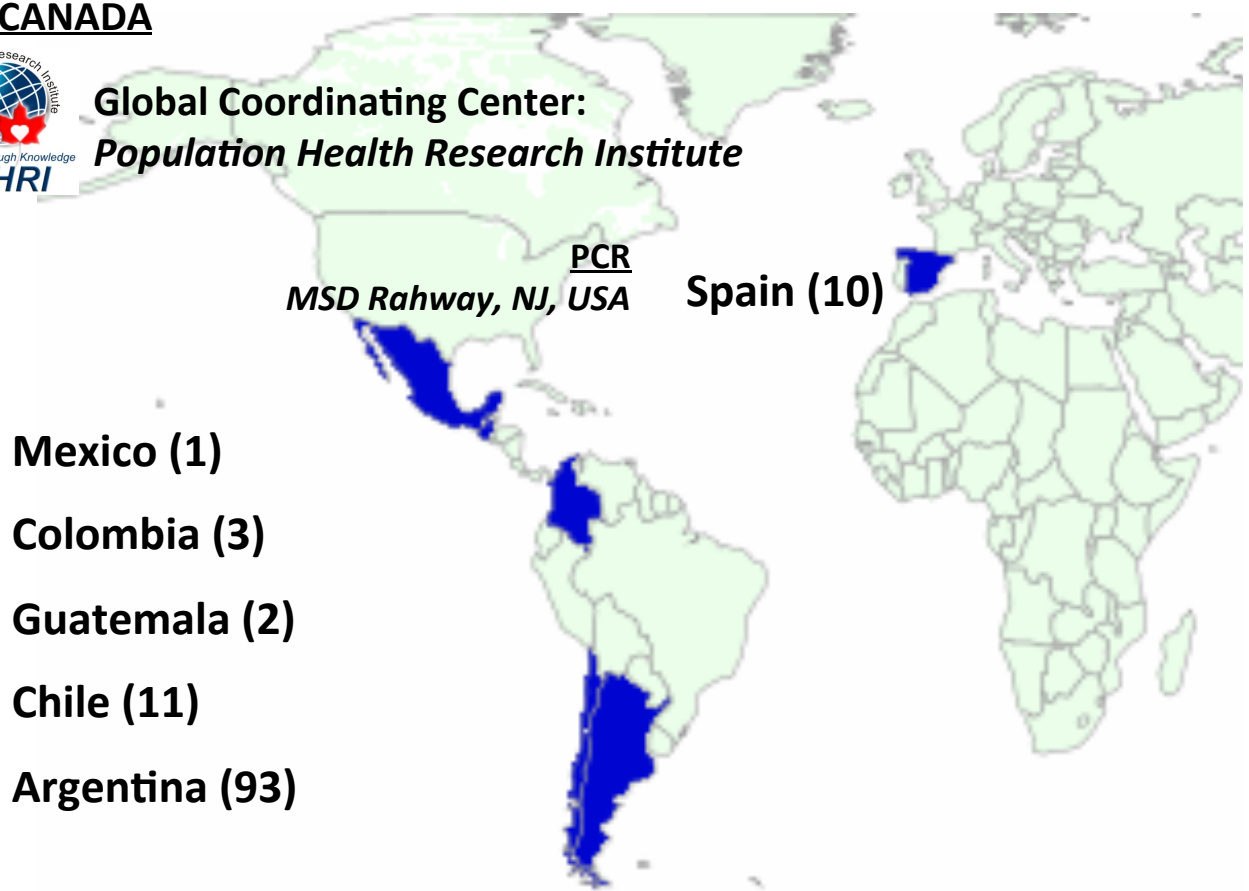
A randomized, active- and placebo-controlled, POS single-blind but BNZ open-label study of a single dose level of POS given either as monotherapy or in combination with BNZ, in subjects with a diagnosis of asymptomatic chronic Chagas disease.

Recruitment

CANADA

Global Coordinating Center:
Population Health Research Institute

PCR
MSD Rahway, NJ, USA



Spain (10)

Mexico (1)

Colombia (3)

Guatemala (2)

Chile (11)

Argentina (93)

6 Countries

19 Centres

393 Screened

120 Randomized

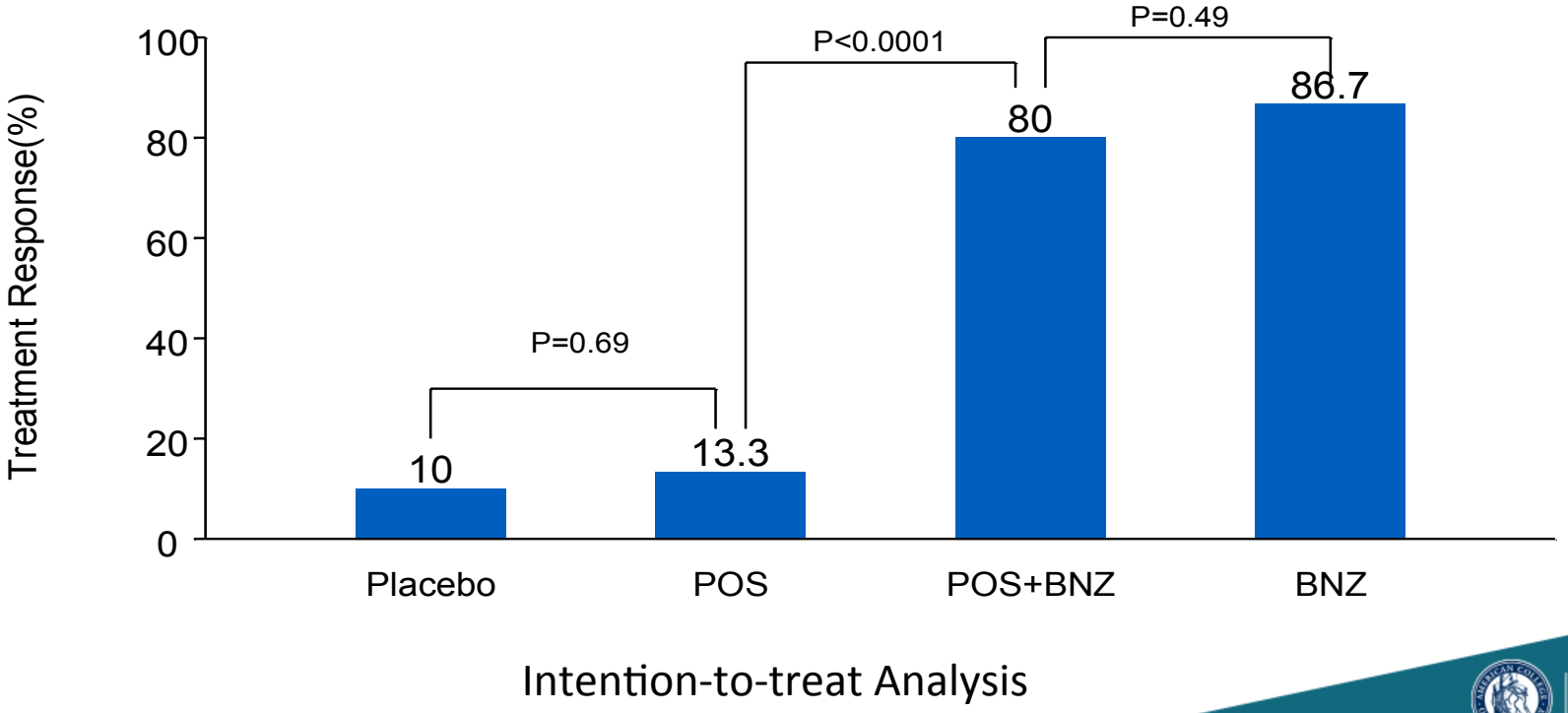
between 2011-2013

Baseline Characteristics

Characteristic	Posaconazole N = 30	Benznidazole N = 30	POS + BNZ N = 30	Placebo N= 30	P Value
Gender (male %)	50%	43.3%	53.3%	76.7%	0.0524
Mean Age (years)	38.7	38.1	37.6	38.7	
BMI	28.0	28.5	27.6	27.8	
LVEF%	64.6 ±7.0	65.2±7.2	63.9±8.7	66.9±8.3	0.5136
PR Interval ms	158.6±22	155.2±21.1	159.8±19.2	161.7±19.2	0.6617
QTc (Bazzett) ms	419.4±19.4	421.1±18.6	420±14.7	412.3±20.7	0.2253

Primary Outcome

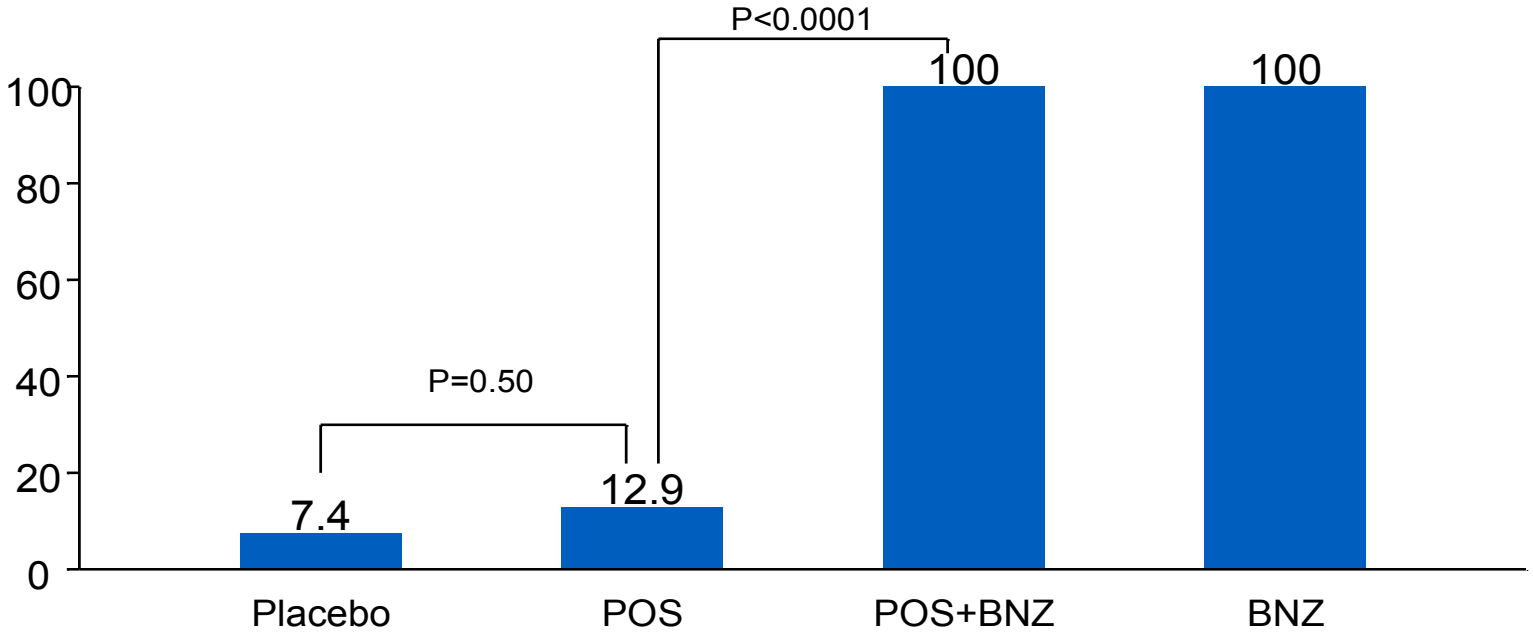
Proportion of subjects with persistent negative RT-PCR by day 180



Intention-to-treat Analysis

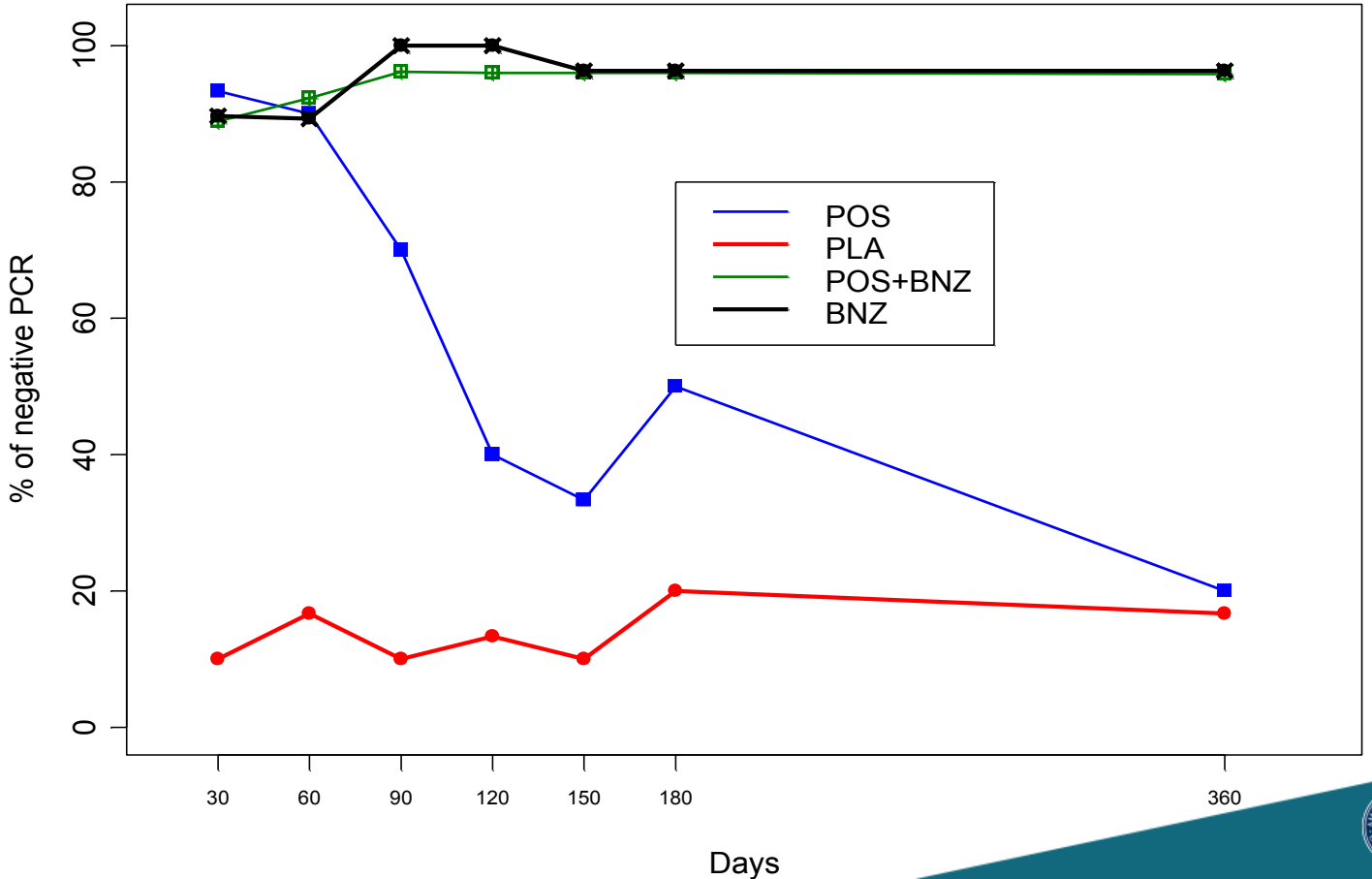
Primary Outcome

Proportion of subjects with persistent negative RT-PCR by day 180



Per-protocol Analysis

RT-PCR Treatment response



Safety Outcomes

	POS N (%)	Placebo N (%)	POS+BNZ N (%)	BNZ+Pla N (%)	P Value
Treated Patients (N)	32	30	28	30	
Any adverse event	20 (62.5)	15 (50.0)	22 (78.6)	26 (86.7)	0.010
Cutaneous reactions	2 (6.3)	3 (10.0)	12 (42.9)	18 (60.0)	<0.0001
Gastrointestinal disorders	12 (37.5)	5 (16.7)	10 (35.7)	8 (26.7)	0.260
Nervous system disorders	4 (12.5)	3 (10.0)	9 (32.1)	10 (33.3)	0.042
Randomized Patients (N)	30	30	30	30	
Permanent discontinuation of POS/PLA	0	1 (3.3)	9 (30.0)	10 (33.3)	
Permanent discontinuation of BNZ	-	-	9 (30.0)	10 (33.3)	

Conclusions

- POS demonstrated significant trypanostatic action against T. cruzi infected asymptomatic carries but no sustained trypanocidal effect was demonstrated.

- Monotherapy with Benznidazole is superior to Posaconazole with high RT-PCR (>90%) conversion rates that are sustained at 1 year.

- Combination therapy did not provide any further efficacy or safety advantages compared to Benznidazole monotherapy.

- Benznidazole trypanocidal activity was strong and by 30-days of treatment therapeutic response was > 90% with few treatment failures that were sustained at 1 year.

Conclusions

- Permanent Benznidazole discontinuation was high (32%).

- These findings suggest that shorter treatment durations i.e. 30-days should be assessed and lower Benznidazole doses tested possibly in combination with newer trypanocidal agents.

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Steering Committee:

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Data Monitoring Committee

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