New & Emerging MS Therapies

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GALA Study- Phase III
40 mg of Glatiramer Acetate SC TIW vs Placebo

Eligible patients

- Aged 18–55 years RRMS (revised McDonald criteria[1])
- EDSS score of ≤5.5
- Relapse free ≤30 days

GA 40 mg tiw (N=943)

Placebo tiw (N=461)

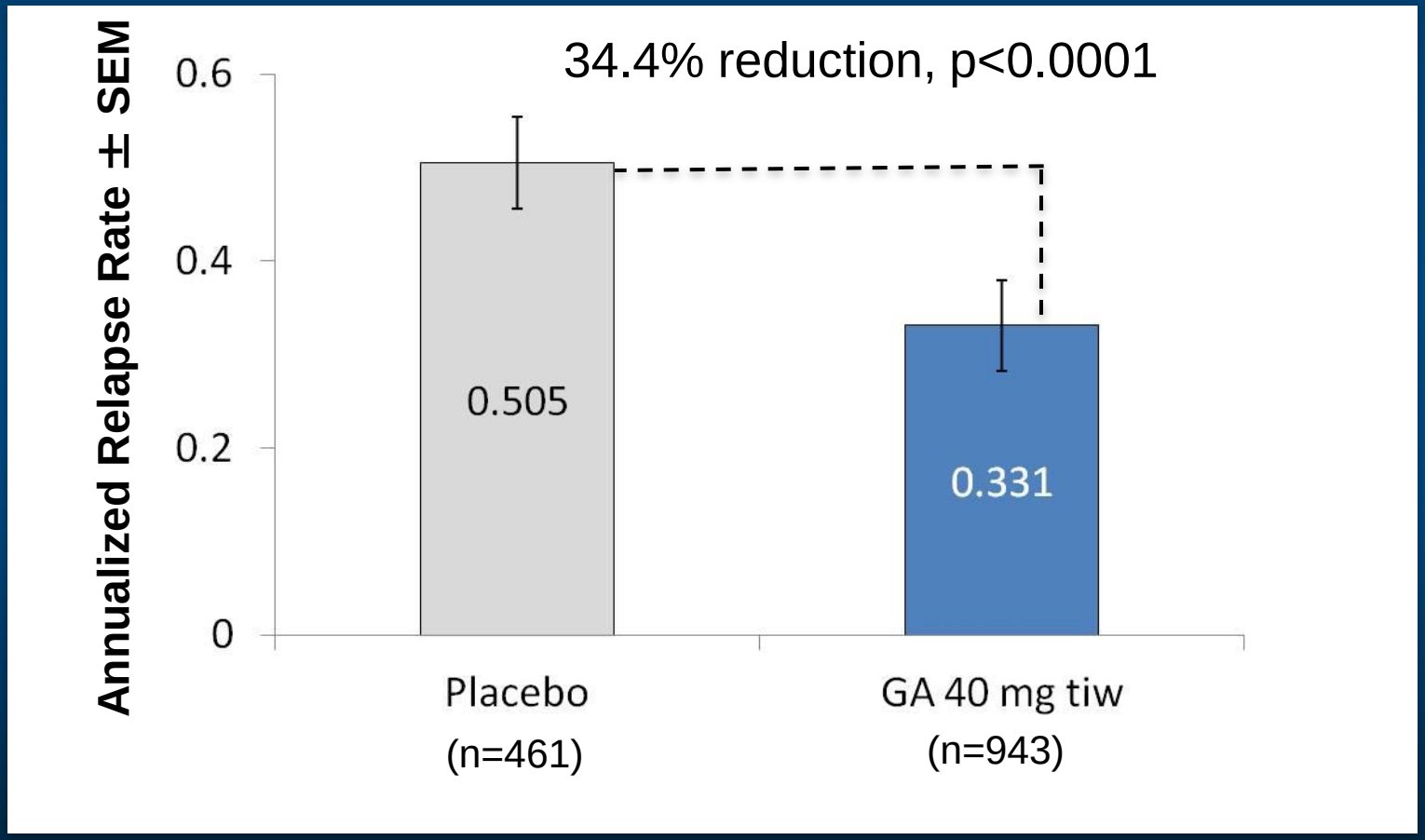
Open-label phase- 40mg tiw (all subjects)

Screening*

Placebo-controlled phase*,† (Randomization 2:1)

Khan, et al., Ann Neurol. 2013 Jun;73(6):705-13

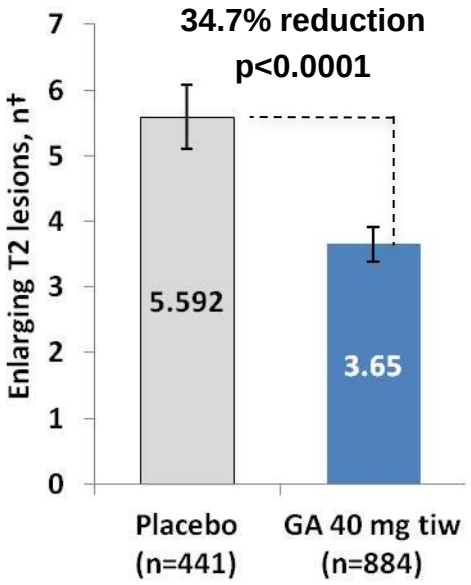
GALA Primary Outcome: Reduction in Annualized Relapse Rate over 12 months



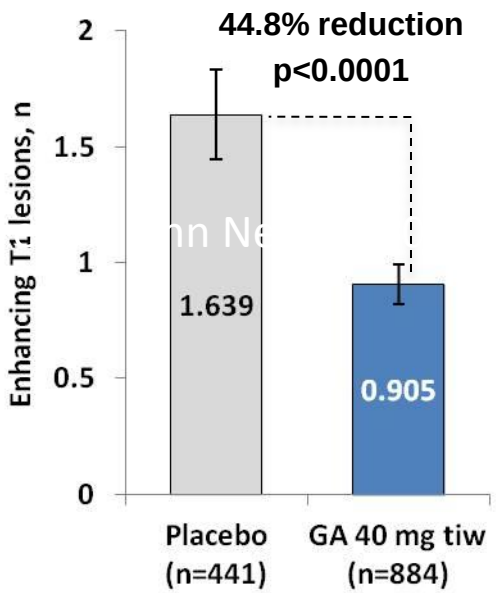
Khan, et al., Ann Neurol. 2013 Jun;73(6):705-13

GALA Secondary MRI Endpoints

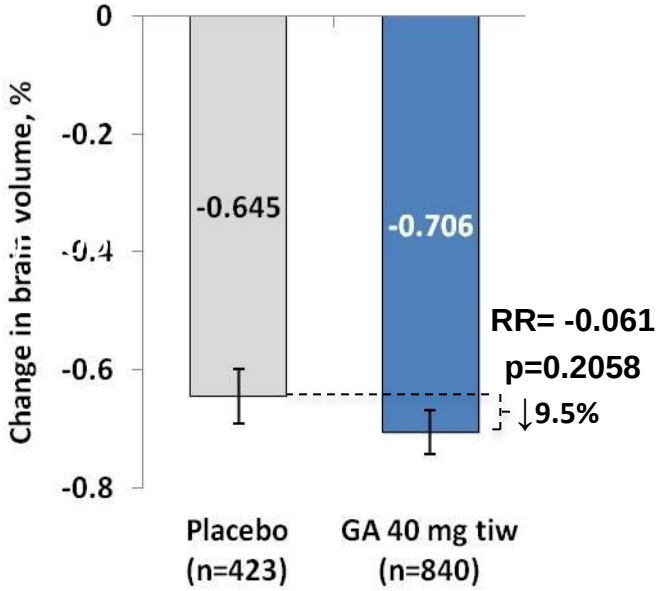
Cumulative number of New/enlarging T2 lesions†



Cumulative number of enhancing T1 lesions†



Percent Change in Brain Volume from Baseline to Month 12‡



Khan, et al., Ann Neurol. 2013 Jun;73(6):705-13

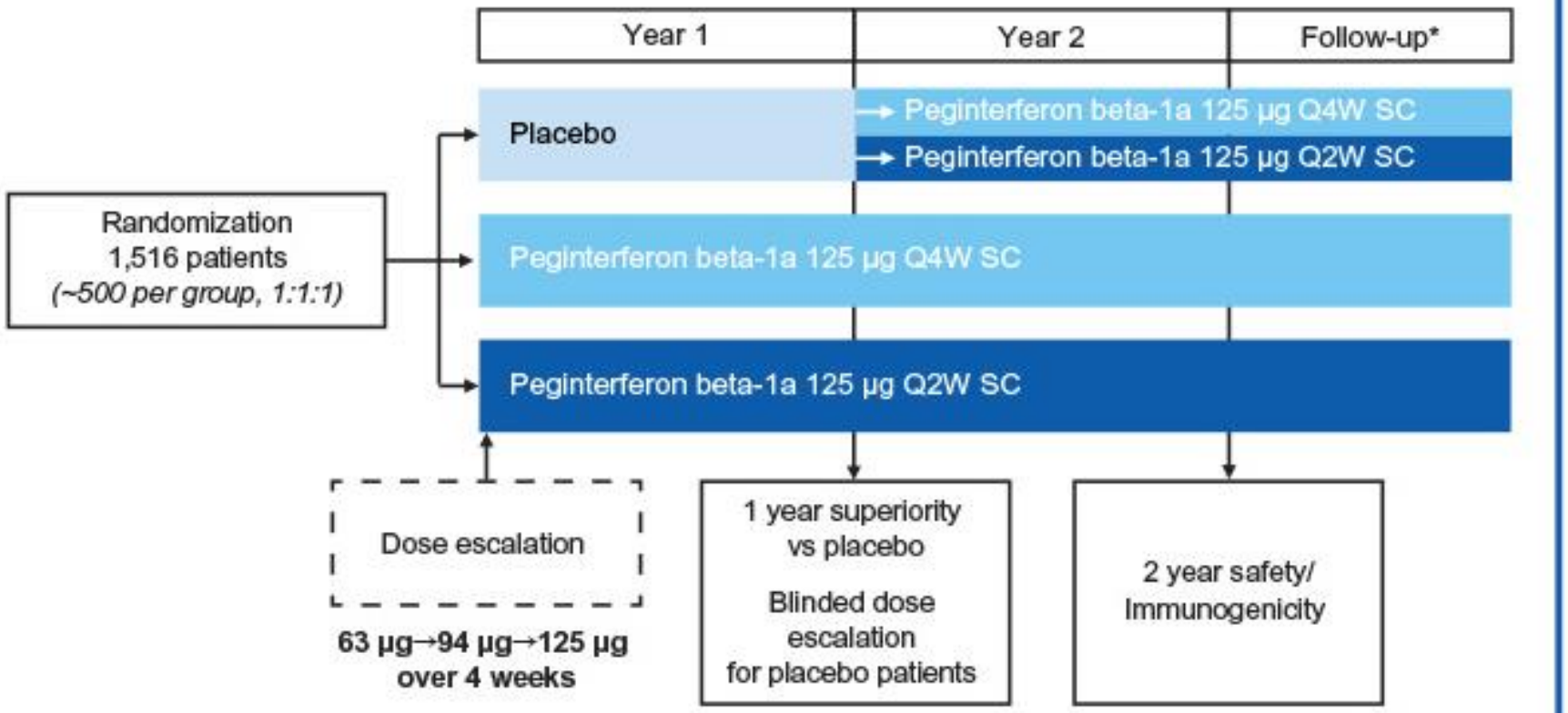
GALA: Adverse Events

	Placebo N=461(%)	GA 40 mg TIW N=943(%)	Original Phase III study [1] GA 20 mg SC daily n=201 (%)
AE	284 (61.6)	680 (72.1)	
Serious AE*	21 (4.6)	42 (4.5)	
AEs occurring in ≥5% in either treatment group			
Injection site erythmea	7 (1.5)	197 (20.9)	132 (66)
Nasopharyngitis	39 (8.5)	100 (10.6)	
Injection site pain	9 (2.0)	98 (10.4)	147 (73)
Headache	55 (11.9)	95 (10.1)	
Injection site pruritus	0 (0)	56 (5.9)	80 (40)
Urinary tract infection	23 (5.0)	46 (4.9)	
Upper respiratory tract infections	25 (5.4)	42 (4.5)	

*One patient death (cardiopulmonary failure) was reported in the placebo group

1. Johnson KP, *et al. Neurology* 1998;50:701–708; Khan, et al., Ann Neurol. 2013 Jun;73(6):705-13

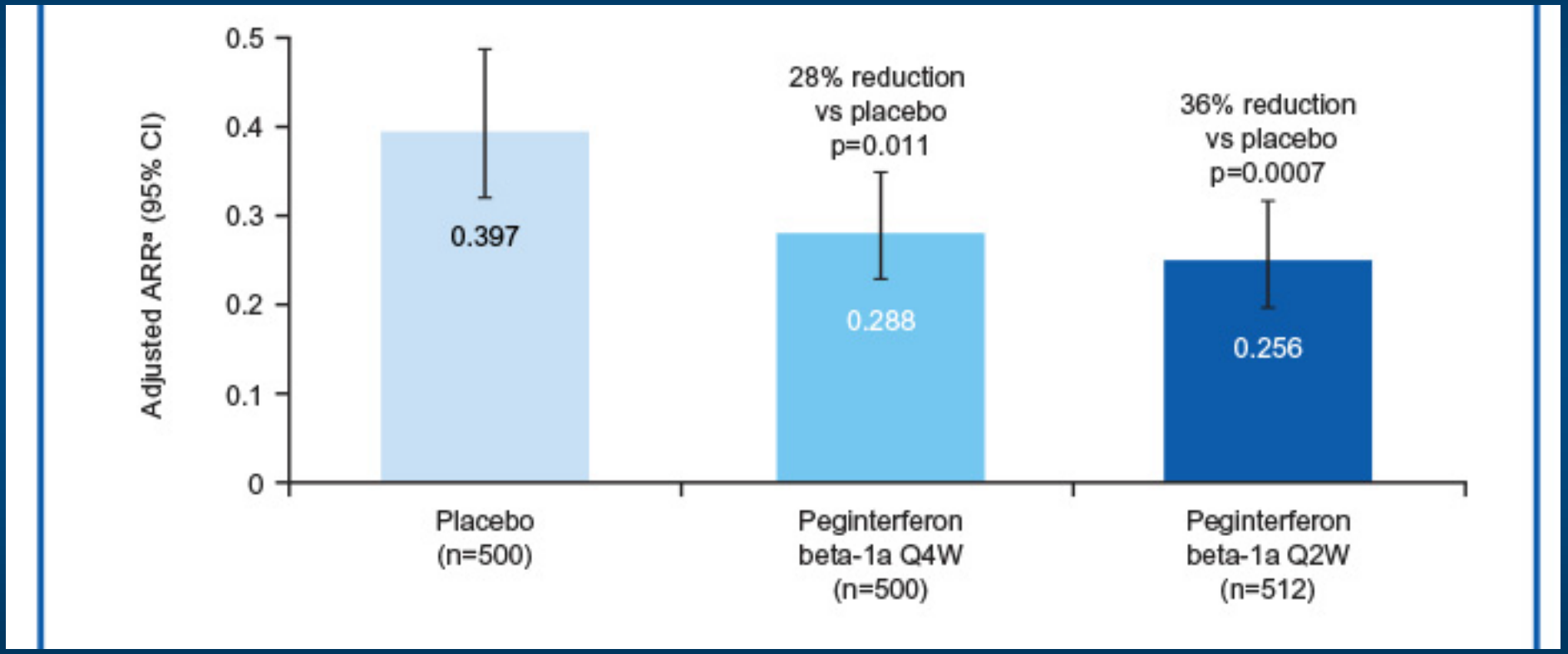
Advance Study: Global, 2-year, randomized, double-blind, PB-controlled efficacy and safety study of subcutaneous PEG-IFNβ-1a 125µg



*12-week safety follow-up period for those subjects who do not enter an extension study (ATTAIN);
Q2W = every 2 weeks; Q4W = every 4 weeks; SC = subcutaneous.

Calabresi P, et al. ECTRIMS 2013; Copenhagen.

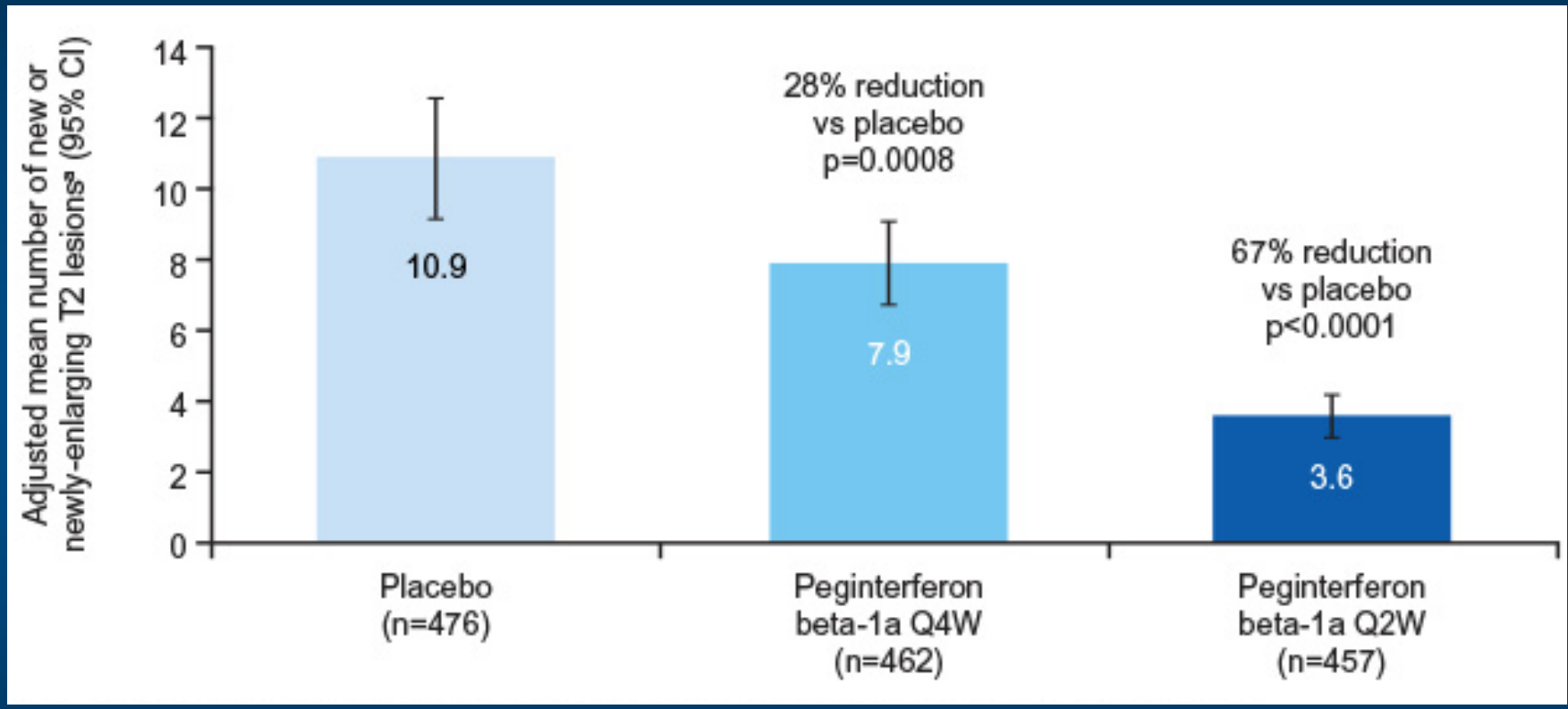
Advance Study Primary Outcome: Annualized Relapse Rate in 12 months



Calabresi P, et al. ECTRIMS 2013; Copenhagen.

Advance Study Secondary MRI Endpoints

T2 Lesion Reduction



T1 Hypointense Lesion Reduction **Q2W= 53%** **p<0.0001** **Q4W= 18% [NS]**

GAD + Lesion Reduction **Q2W= 86%** **p<0.0001** **Q4W= 36% [NS]**

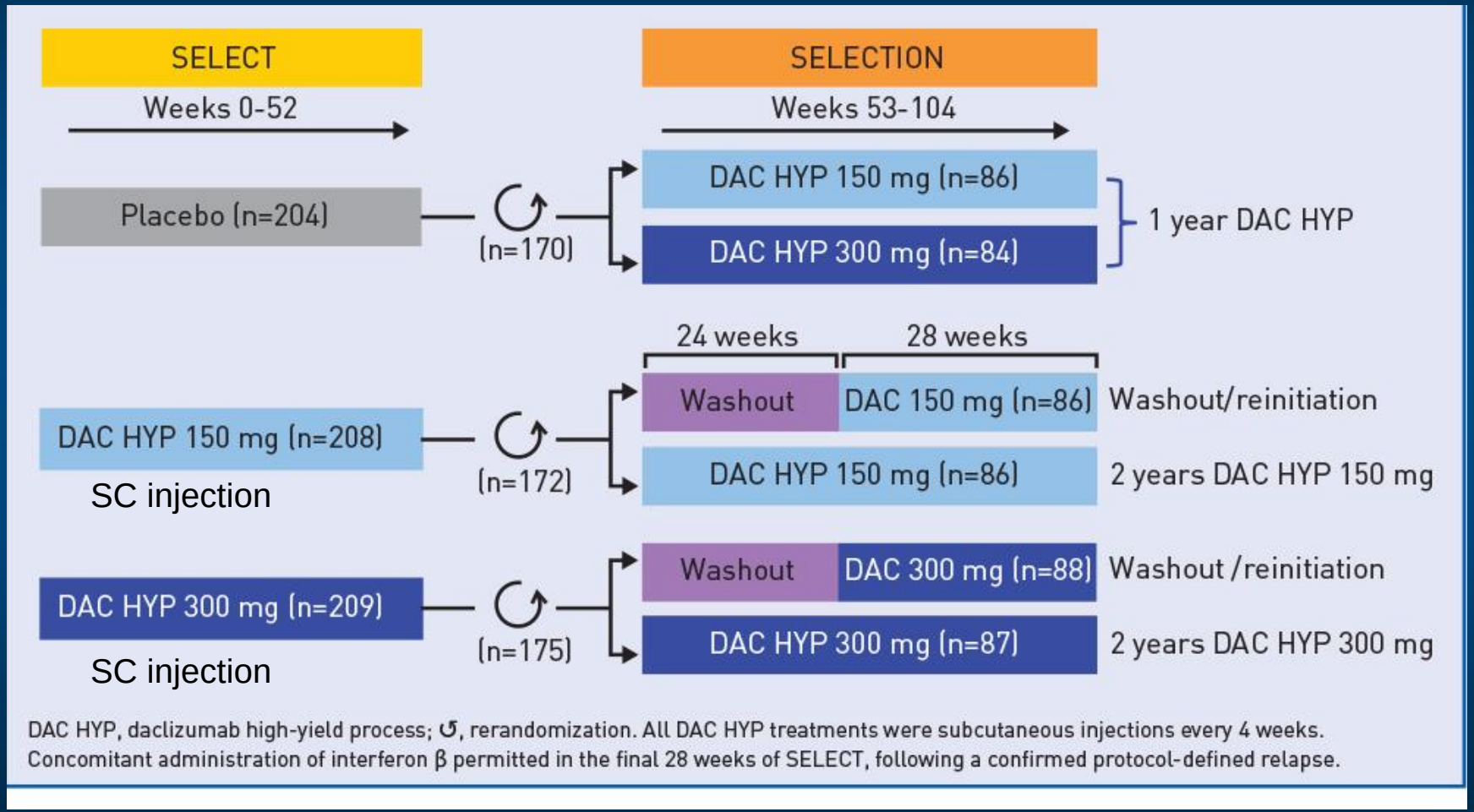
Calabresi P, et al. ECTRIMS 2013; Copenhagen.

Advance Study: Side Effects

	Placebo N=500(%)	125µ PegIFN SC Q4W N=500(%)	125µ PegIFN SQ Q2W N=512(%)	Original Phase III study* IFN IM QW N=351(%)
AE	417 (61.6)	472 (94)	481(94)	
Serious AE*	76 (15)	71 (14)	55(11)	
AEs occurring in ≥20% in any treatment group				
Injection site erythmea	33 (7)	282 (56)	315 (62)	(6) inflam
Influenza-like illness	63 (13)	234 (47)	230 (47)	171 (49)
Pyrexia	76 (15)	218 (44)	228 (45)	70 (20)
Headache	165 (33)	204 (41)	224 (44)	203 (58)
MS Relapse	159 (32)	111 (22)	96 (19)	

Calabresi P, et al. ECTRIMS 2013; Copenhagen.
Kieseier B, et al. ECTRIMS 2013; Copenhagen.
*Avonex Package Insert, 2003

Daclizumab Phase II
Select and Selection (Ext) Study



DAC HYP, daclizumab high-yield process; ↺, rerandomization. All DAC HYP treatments were subcutaneous injections every 4 weeks. Concomitant administration of interferon β permitted in the final 28 weeks of SELECT, following a confirmed protocol-defined relapse.

Giovannoni G, et al. Presented at: 65th Annual Meeting of the American Academy of Neurology; March 16-23, 2012; San Diego, CA. *Neurology*. 2013;80: S01.001

SELECT and SELECTION Results

- **Results of Select**
  - 59% Reduction in relapse rate vs Placebo
  - T1 hypo-intense lesions decrease by 14% compared to placebo
  - 79% Reduction of new or enlarging T2 lesions

- **Patients who remained on DAC HYP over 2 yrs**
  - ARR reduction in yr 1 sustained in yr 2 (0.148 vs. 0.165)
  - 88% free of confirmed disability progression at yr 2
  - Fewer new T2 lesions in yr 2 vs. yr 1 (*P*=0.032)
  - Rate of Brain Atrophy reduced in the second year of tx

Giovannoni G, et al. Presented at: 65th Annual Meeting of the American Academy of Neurology; March 16-23, 2012; San Diego, CA. *Neurology*. 2013;80: S01.001; Radue E, et al. ECTRIMS 2013; Copenhagen. [P525]; Radue E, et al. ECTRIMS 2013; Copenhagen. [P977]

SELECTION Extension Study: Safety

	SELECTION vs. SELECT		
Serious infections:	13 (2%)	vs.	13 (2%)
Serious skin events:	6 (1.1%)	vs.	(1.0%)
New LFT abnorm >5x ULN:	8 (1.5%)	vs.	(4%)

- One patient in daclizumab high yield process (DAC HYP) 300 mg washout/re-initiation group died from autoimmune hepatitis after re-initiation
- No MRI rebound effect observed during the washout

Giovannoni G, et al. Presented at: 65th Annual Meeting of the American Academy of Neurology; March 16-23, 2012; San Diego, CA. Neurology. 2013;80: S01.001.

Week 144 Results of a Phase II, Randomized, Multicenter Trial Assessing the Safety and Efficacy of Ocrelizumab in Patients with Relapsing–Remitting Multiple Sclerosis (RRMS)

Cycle	Group 1	Group 2	Group 3	Group4
Cycle 1: 0-24 weeks	Placebo	OCR 600 mg	OCR 2000 mg	Interferon-β
Cycle 2: 24-48 weeks	OCR 600 mg	OCR 600 mg	OCR 1000 mg	OCR 600 mg
Cycle 3: 48-72 weeks	OCR 600 mg	OCR 600 mg	OCR 1000 mg	OCR 600 mg
Cycle 4: 72-96 weeks	OCR 600 mg	OCR 600 mg	OCR 600 mg	OCR 600 mg

Ocrelizumab Phase II Study Results

- Ocrelizumab (OCR) reduced Gd+ lesions by 89% at 24 wks
  - Low MRI activity maintained through wks 96 to 144
  - 72 weeks after last infusion very little MRI activity observed
- ARR:
  - OCR reduced ARR by 73% vs. placebo at week 24[1]
  - ARR for OCR 600 mg after >3 cycles: 0.035-0.189 for wks. 96-144

1. Hauser, S et al. Presented at: 65th Annual Meeting of the American Academy of Neurology; Mar 16-23, 2013; San Diego, CA. *Neurology*, 2013; S31.004; http://www.medscape.com/viewarticle/781671. Accessed March 29,2013.

Ocrelizumab Phase II Study: Safety

- Rates of AE's, SAE's and serious infections were similar between placebo and both doses of OCR during study
- Adverse Events (AEs) during **active phase**
  - Majority of patient withdrawals occurred in first cycle (0-24 wks) due to infusion reactions[1]
  - One death in 2000 mg ocrelizumab (OCR) group at wk 4 due to systemic inflammatory response[1-3]
- AEs during the **extension phase**
  - 67-78% of patients completed at wk 144[1]
  - 2 patients died who received OCR (neither related to OCR and both had B-cells return w/in normal limits)

Endpoint	PBO/OCR	Low-Dose OCR	High-Dose OCR	Interferon-β/OCR
Serious AEs (n)	Injury:1	Salivary duct inflammation: 1	Muscle weakness: 1 Breast cancer: 1 Acute psychosis: 1 Suicidal ideation: 1	Drug-withdrawal syndrome: 1
Infections (n)	13	12	13	9

1. Hauser S, et al. Presented at: 65th Annual Meeting of the American Academy of Neurology; March 16-23, 2013; San Diego, CA. *Neurology*. 2013;80: S31.004. 2. Kappos L, et al. *Lancet*. 2011;378:1779-1787. 3. http://www.medscape.com/viewarticle/781671. Accessed March 29,2013

Thank you for your attendance!