

CONTEMPORARY CLINICAL ISSUES AND CASE STUDIES

PLENARY SESSION



Daclizumab in Patients with Active Relapsing Multiple Sclerosis on Concurrent Interferon-beta Therapy Week 44 Data Phase II (CHOICE) Study

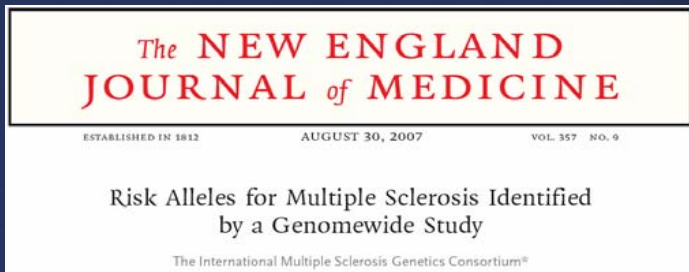
M. Kaufman (North Carolina, USA), D. Wynn
(Illinois, USA), X. Montalban (Barcelona, Spain)
on behalf of the CHOICE investigators

Director, MS Center, Carolinas Medical Center

Michael.kaufman@carolinashealthcare.org

Study funded by PDL BioPharma and Biogen Idec

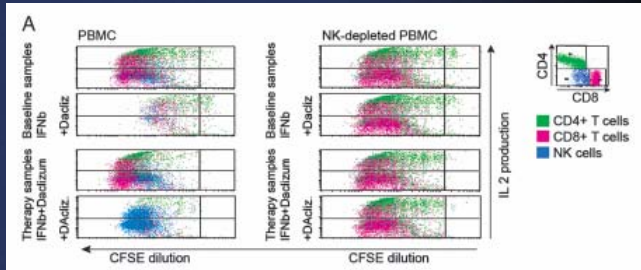
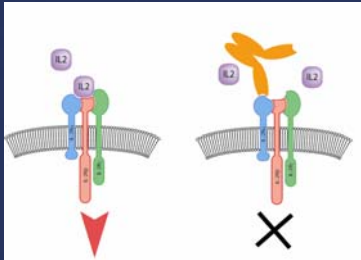
CD25 (IL-2R α) Interesting from a Genetic Perspective



CD25 polymorphisms ($P=2.96 \times 10^{-8}$) are the strongest predictors of MS risk after those of the HLA locus ($P=8.94 \times 10^{-81}$).

Mechanisms of Anti-human IL-2 Receptor Alpha (IL-2R α) Chain Action

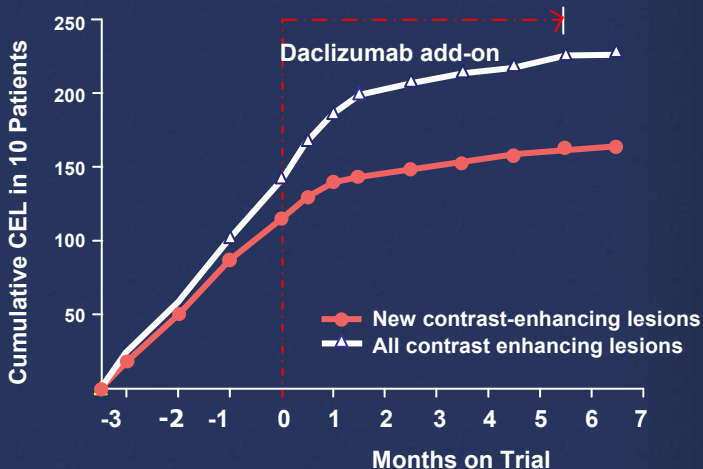
- Daclizumab: Approved for the prevention of renal allograft rejection as Zenapax[®]
- Humanized anti-human IL-2R α (CD25, TAC) antibody; 90% Human – 10% Mouse (CDR)
- Binds to CD25 preventing IL-2 engaging the alpha chain of the high affinity IL-2 Receptor and the consequent activation of T cells
- Down modulates IL-2R α on activated T cells
- Expands CD56^{bright} NK cell clones, which are thought to kill activated T cells*



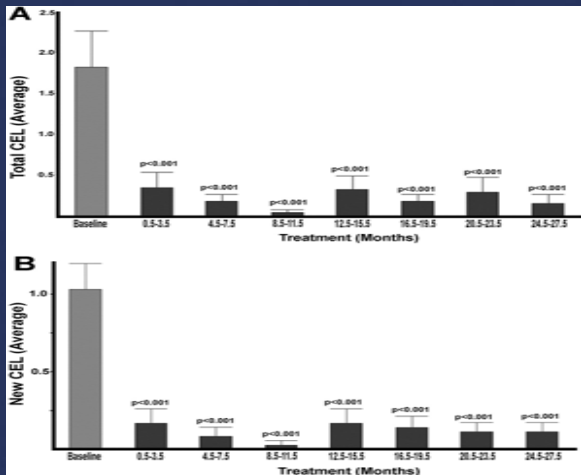
*Bielekova et al. *Proc Natl Acad Sci USA* 2006;103:5941-6.

NIH Pilot Daclizumab Study in MS

Primary endpoint: cumulative contrast-enhancing lesions (CEL)



Open-label Trial of IFN β + Daclizumab



CHOICE Study Design

- Multicenter, randomized, double-blind, placebo-controlled
- 230 patients active, relapsing forms of MS despite treatment with IFN β
- 51 sites in North America and Europe
- 24-week treatment period with 48-week wash-out
- Regimen: 3 arms randomized 1:1:1
 - DAC 2 mg/kg SC q 2 weeks (11 doses) + IFN β
 - DAC 1 mg/kg SC q 4 weeks (6 doses) + IFN β ; alternates with placebo q 2 weeks
 - Placebo SC q 2 weeks + IFN β

CHOICE Study Design

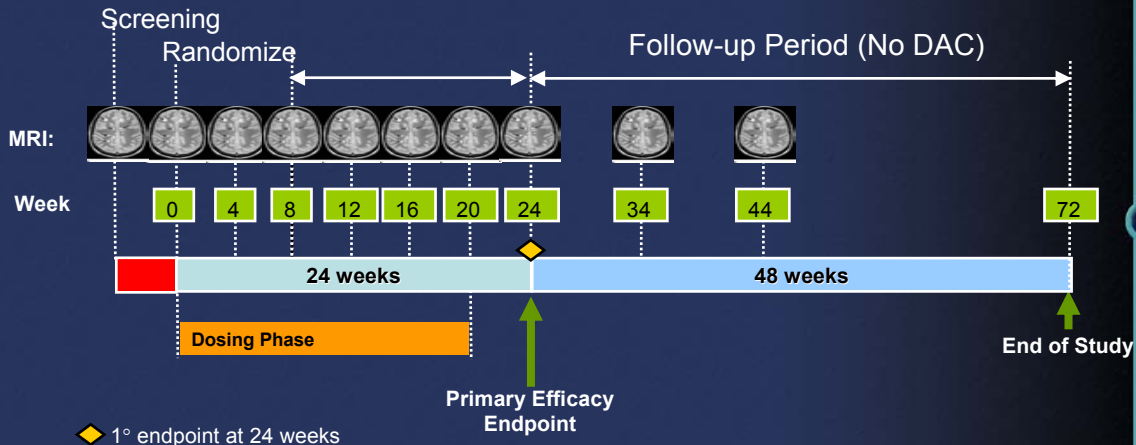
Key inclusion criteria

- MS (McDonald), 18-55 years
- EDSS \leq 5.0
- Stable IFN β regimen for \geq 6 months
- MRI with Gd+ lesion *or* at least one relapse in past 12 months

Key endpoints

- Primary: New or enlarged Gd+ lesions between Weeks 8 and 24, adjusted by total number of baseline lesions and type of MS
- Secondary:
 - Relapse rate between Weeks 8 and 24
 - Safety

CHOICE Study Design



All patients on background IFN-beta

CHOICE DSMB

Stephen C. Reingold, Chair New York City, New York

Gary Cutter Birmingham, Alabama

Gilles Edan Rennes, France

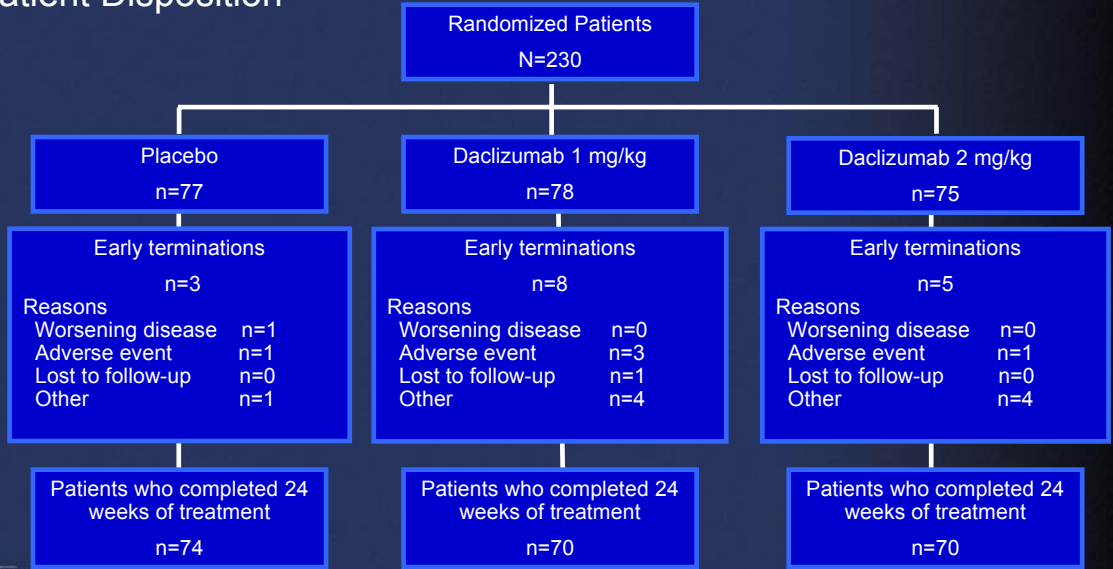
Mark Freedman Ottawa, Ontario, Canada

Jerry Wolinsky Houston, Texas

Central MRI Reading Center

Jack Simon UC BIRL, Denver, Colorado

Patient Disposition



90% completed treatment period

Baseline Demographics

	Placebo n=77	DAC 1 mg/kg n=78	DAC 2 mg/kg n=75
Age, y Mean	40.8	38.2	40.4
Male, %	28.6	25.6	22.7
Time since 1 st symptoms, y Mean (SD)	9.6 (6.8)	9.3 (6.8)	9.5 (6.9)
RRMS, n (%)	72 (94%)	71 (91%)	69 (92%)
EDSS, mean (SD) Median (range)	3.0 (1.2) 3.0 (0, 6.0)	3.0 (1.2) 3.0 (0, 6.0)	3.0 (1.3) 3.0 (0, 6.5)

RRMS = relapsing-remitting MS; EDSS = Expanded Disability Status Scale.

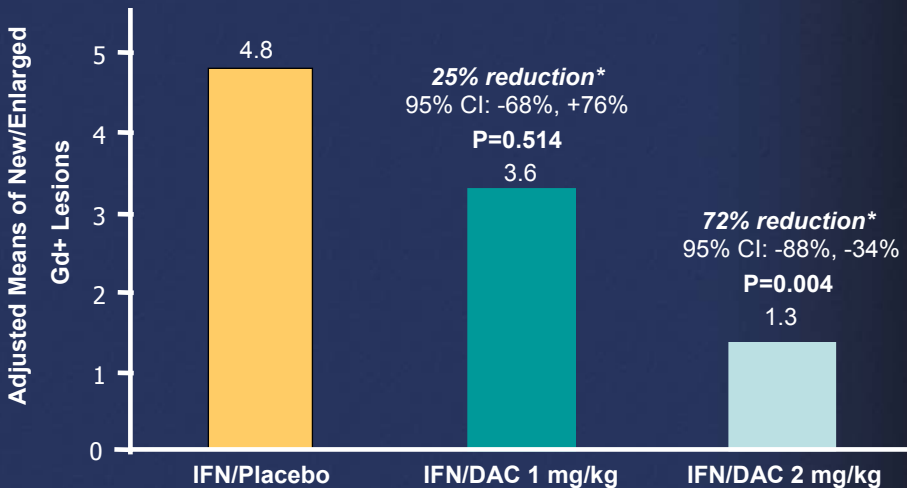
No statistically significant difference between DAC 1 mg/kg vs Placebo and DAC 2 mg/kg vs Placebo, separately.

Baseline Disease Characteristics

	Placebo n=77	DAC 1 mg/kg n=78	DAC 2 mg/kg n=75
Number of Gd+ lesions (%)			
0	49 (64)	42 (54)	52 (69)
1	17 (22)	11 (14)	10 (13)
2	0	7 (9)	6 (8)
3	1 (1)	4 (5)	2 (3)
≥4	9 (12)	14 (18)	5 (7)
Missing	1 (1)	0	0
Mean (SD)	1.1 (2.7)	2.7 (7.0)*	0.8 (1.7)
Median (range)	0 (0, 16)	0 (0, 51)	0 (0, 10)
No. of relapses prior 2 y (SD)	2.6 (1.7)	2.6 (1.6)	2.4 (1.2)
Median (range)	2.0 (0, 10)	2.0 (0, 7)	2.0 (0, 5)

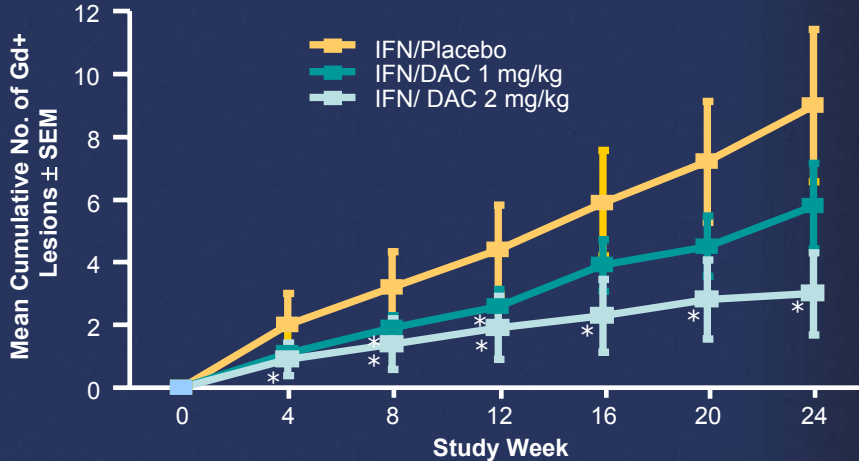
Gd+ = gadolinium-enhancing; *P<0.05, Dac 1 mg/kg vs. Placebo.

Primary Endpoint – Adjusted New or Enlarged Gd+ Lesions



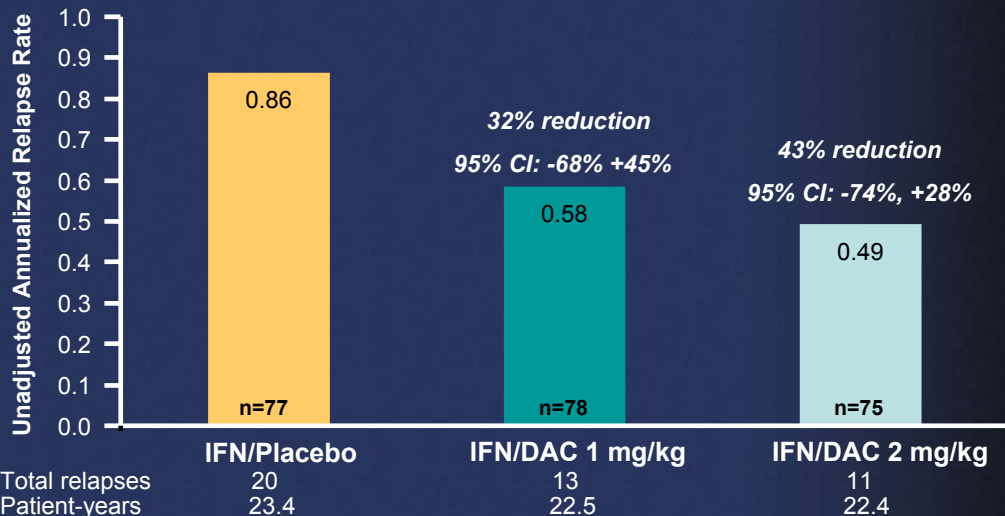
*P-values, percent reductions, and 95% confidence intervals were estimated from a negative binomial regression adjusting for the number of baseline lesions and type of MS (RRMS vs. SPMS).

Cumulative Number of New or Enlarged Gd+ Lesions by Visit

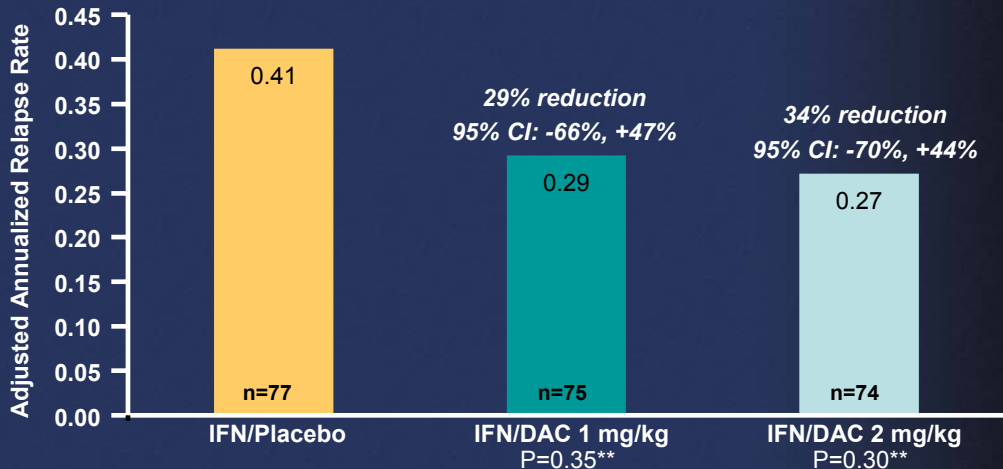


*P<0.05 vs. placebo. P-values were estimated from a negative binomial model adjusting for the total number of baseline lesions.

Secondary Endpoint: Unadjusted Annualized Relapse Rate Weeks 8-24

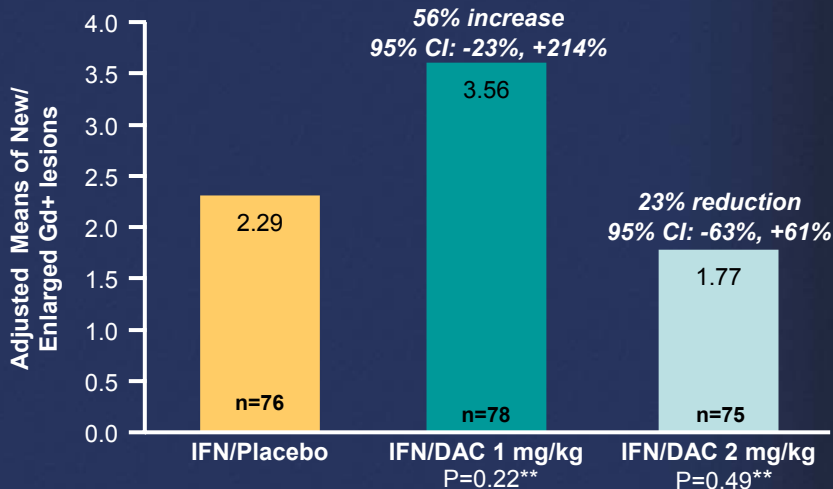


Secondary Endpoint: Adjusted Annualized Relapse Rate* Weeks 8-24



*Estimated from a Poisson regression model adjusting for the number of relapses in the 2 years prior to randomization and baseline disease status; **Compared with placebo.

Effects of Daclizumab Appeared Reversible Within ~3 Months of Discontinuing Therapy*



*Between 10 - 20 weeks after stopping daclizumab; **Estimated from a negative binomial model adjusted for the no. of Gd lesions at baseline and baseline disease status.

Safety Summary

	Placebo n=77	DAC 1 mg/kg n=78	DAC 2 mg/kg n=75
<i>Any Adverse Event</i>	75 (97.4)	78 (100)	71 (94.7)
<i>Serious Adverse Events</i>			
Any SAE	4 (5.2)	9 (11.5)	11 (14.7)
<i>Selected Adverse Events</i>			
Injection Site Reactions	34 (44.2)	30 (38.5)	26 (34.7)
Any Cutaneous Event	20 (26)	35 (44.9)	24 (32)
Grade 3/4 Cutaneous Events	0 (0.0)	1 (1.3)	2 (2.7)

* Data presented as n (%)

Safety Summary

	Placebo n=77	DAC 1 mg/kg n=78	DAC 2 mg/kg n=75
Overall Infections	53 (68.8)	54 (69.2)	51 (68.0)
Any Serious Infection	1 (1.3)	2 (2.6)	5 (6.7)
Grade 3/4 serious infections	1 (1.3)	2 (2.6)	4 (5.3)
Opportunistic Infections	0 (0.0)	0 (0.0)	0 (0.0)

* Data presented as n (%)

Conclusions

- CHOICE provides proof-of-concept for an anti-CD25 strategy in MS
- Daclizumab substantially reduced the number of new or enlarged Gd+ lesions at 2 mg/kg in patients not controlled with IFN-beta therapy
- Overall results support moving forward into larger studies to establish long-term safety and efficacy of daclizumab in MS

CHOICE Investigators

J. Absher	Absher Neurology, P.A.	Greenville, SC
T. Arbizu	Bellvitge University Hospital	Barcelona, Spain
G. Blevins	University of Alberta	Edmonton, Alberta, Canada
J. Carter	Mayo Clinic	Scottsdale, AZ
B. Casanova	La Fe University Hospital	Valencia, Spain
G. Comi	University of Milan	Milano, Italy
J. Cooper	Alta Bates Summit Medical Center	Berkley, CA
R. Dickson	Wenatchee Valley Medical Center	Wenatchee, WA
J. Dunn	MS Center at Evergreen	Kirkland, WA
K. Edwards	Neurological Research Center, Inc.	Bennington, VT
J. English	The Multiple Sclerosis Center of Atlanta	Atlanta, GA
O. Fernandez	Carlos Haya University Hospital	Malaga, Spain
C. Ford	Mind Imaging Center	Albuquerque, NM
E. Fox	Central Texas Neurology	Round Rock, TX
M. Freedman	Raleigh Neurology Associates	Raleigh, NC
P. Gallo	The Multiple Sclerosis Centre of the Veneto Region	Padova, Italy
A. Garcia-Moreno	Servicio De Neurologia	Madrid, Spain
M. Gottesman	Winthrop University Hospital	Mineola, NY
C. Heesen	University of Hamburg	Hamburg, Germany
J. Herbert	Hospital for Joint Diseases, MS Care Center	New York, NY
W. Honeycutt	Neurology Associates, P.A.	Maitland, FL
A. Jacobs	Neurology Specialists	Dayton, OH
F. Jacques	CHVO Hopital de Hull	Gatineau, PQCanada
D. Jeffrey	Wake Forest University, Health Services	Winston-Salem, NC
L. Kasper	MS Center at Dartmouth	Lebanon, NH

CHOICE Investigators

M. Kaufman	Neuroscience & Spine Institute	Charlotte, NC
O. Kahn	Wayne State University MS Center	Detroit, MI
B. Khatri	Center for Neurological Disorders	Milwaukee, WI
M. Kremenchutzky	London Health Sciences Centre	London, Ontario, Canada
Y. Lapierre	Montreal Neurological Institute	Montreal, Quebec, Canada
S. Lynch	KUMC Neurology	Kansas City, KS
C. Markowitz	University of Pennsylvania	Philadelphia, PA
J. Martin	Michigan State University	East Lansing, MI
M. Melanson	Health Sciences Center	Winnipeg, Manitoba, Canada
A. Minagar	Louisiana State University Health Sciences Center	Shreveport, LA
X. Montalban	Hospitals Vall D'Hebron	Barcelona, Spain
P. O'Connor	St. Michael's Hospital	Toronto, Ontario, Canada
T. Phillips	The MS Center at Texas	Dallas, TX
M. Picone	GIMBEL MS Center	Teaneck, NJ
I. Pirko	University of Cincinnati	Cincinnati, OH
C. Pozilli	Azienda Ospedaliera Sant'Andrea	Roma, Italy
S. Pugh	Rockwood Clinic, P.S.	Spokane, WA
J. Rose	University of Utah CAMT	Salt Lake City, UT
N. Sommer	Philipps University	Marburg, Germany
B. Steingo	Neurological Associates	Pompano Beach, FL
J. Storey	Upstate Clinical Research	Albany, NY
H. Sullivan	Michigan Medical P.C.	Grand Rapids, MI
F. Thomas	St. Louis University Hospital	St. Louis, MO
T. Vollmer	St. Joseph's Hospital and Medical Center	Phoenix, AZ
K. Wadinger	Charite Campus Mitte	Berlin, Germany
D. Wynn	Consultants in Neurology	Northbrook, IL