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American Society of Clinical Oncology Annual Meeting
June 1–5, 2018
Chicago, IL, USA

Adverse Events of Special Interest in the Phase 3 COLUMBUS Study

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INTRODUCTION

- Activating *BRAF*^{V600} mutations occur in ~50% of patients with melanoma.[1] These mutations drive constitutive activation of the mitogen-activated protein kinase (MAPK) pathway, resulting in the development and progression of melanoma.[2]
- Dual inhibition of the MAPK pathway with combination BRAF/MEK inhibitor (BRAFi/MEKi) therapy is a standard treatment in patients with *BRAF*^{V600}-mutant metastatic melanoma.[3-6]
  - Compared with BRAFi monotherapy, BRAF/MEKi combination therapy improves survival while reducing BRAFi-associated toxicities resulting from paradoxical MAPK pathway activation.[3,7]
  - BRAF/MEKi therapies are associated with characteristic adverse events (AEs), but each of the established combinations (dabrafenib plus trametinib and vemurafenib plus cobimetinib) has a distinct safety profile with unique toxicities that impact overall tolerability and may impact the ability to deliver optimal treatment.
    - Pyrexia has been observed in 51%–53% of patients treated with dabrafenib plus trametinib, and has included serious febrile reactions and multiple episodes. It was the leading cause of dose interruption (30%–32% of patients) or reduction (13%–14% of patients) and discontinuation (2%–3% of patients).[3-4]
    - Photosensitivity has been commonly seen in patients treated with vemurafenib plus cobimetinib, occurring in 48% of patients. The median time to first onset was 2 months, the median duration was 3 months, and photosensitivity recurred in 36% of patients.[5]
- The phase 3 COLUMBUS study is evaluating a third BRAF/MEKi combination, the BRAFi encorafenib plus the MEKi binimetinib, in patients with *BRAF*^{V600}-mutant melanoma.[9]
  - Encorafenib plus binimetinib has shown favorable efficacy, with a median progression-free survival of 14.9 compared with 7.3 months for vemurafenib.[9]
  - In an update of the study, median overall survival was 33.6 months with encorafenib plus binimetinib compared with 16.9 months with vemurafenib.[10]

OBJECTIVES

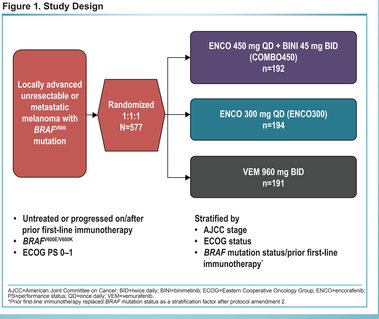
- Here, we report class-based AEs of special interest (AESIs) from the COLUMBUS study. Details are provided for AESIs of particular clinical relevance.

METHODS

Study Design

- Patients were randomized 1:1:1 to receive either encorafenib 450 mg once daily + binimetinib 45 mg twice daily (COMBO450), encorafenib 300 mg once daily (ENCO300), or vemurafenib 960 mg twice daily (VEM; **Figure 1**).

Figure 1. Study Design



METHODS (continued)

Safety Evaluations

- Safety was assessed in all patients who received at least one dose of study drug and had at least one postbaseline safety assessment.
- Safety evaluation included collection of all AEs, physical examinations, ophthalmic and dermatologic examination, cardiac assessments, and clinical laboratory assessments.
  - Ophthalmic examinations were performed at every scheduled visit for all patients in the COMBO450 group and for those in the ENCO300 and VEM groups with retinal abnormalities at baseline.
- The severity of AEs was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 4.03.
- Individual AEs describing similar clinical entities or pathophysiologic processes that represent known effects of available BRAFi and/or MEKi were grouped into AESIs.

Statistical Analysis

- The cutoff date for these analyses was May 19, 2016.
- Time-to-first-onset analyses were conducted only for patients experiencing the event.
- Exposure-adjusted incidence rate (EAIR; per 100 patient-months of exposure to study drug) was calculated for each AESI as the number of patients experiencing the AESI divided by the total exposure-time at risk for the AESI. The duration of study drug exposure contributed by an individual patient was truncated at the time of first onset of the AESI.

RESULTS

Patients

- Demographic and baseline characteristics were generally similar among treatment groups (**Table 1**).

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic	COMBO450 n=192	ENCO300 n=194	VEM n=191
Mean (SD) age, years	56 (14)	55 (13)	55 (14)
Male sex, %	60	56	58
ECOG performance status 0,* %	72	72	73
LDH ≥ULN, %	29	24	27
BRAF mutation status (V600E/V600K), %	89/11	89/10†	88/12
Tumor stage at study entry, %			
IIIB/IIIC	5	3	6
IVM1a	14	15	13
IVM1b	18	20	16
IVM1c	64	62	65
Number of organs involved, %			
1	24	29	24
2	30	27	31
≥3	45	44	46
Prior immunotherapy,‡ %	30	30	30
Ipilimumab	4	5	4
Prior anti–PD-1 or anti–PD-L1	1	1	0
Interferons/interleukins	27	26	27

COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ECOG=Eastern Cooperative Oncology Group; ENCO300=encorafenib 300 mg once daily; LDH=lactate dehydrogenase; PD-1=programmed death 1; PD-L1=programmed death ligand 1; ULN=upper limit of normal; VEM=vemurafenib 960 mg twice daily.
*All other patients had ECOG performance status of 1.
†Two observations were indeterminate.
‡Includes adjuvant and metastatic settings.

RESULTS (continued)

Table 2. AESIs by Incidence and Exposure-Adjusted Incidence Rates*

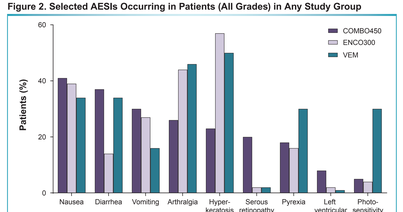
	COMBO450 n=192		ENCO300 n=192		VEM n=186	
	n (%)	EAIR*	n (%)	EAIR*	n (%)	EAIR*
General disorders and administration site conditions						
Fatigue†	83 (43)	5.5	80 (42)	6.8	86 (46)	9.1
Pyrexia‡	35 (18)	1.7	30 (16)	1.9	55 (30)	5.1
Peripheral edema§	25 (13)	1.2	16 (9)	1.1	27 (15)	2.1
Erythema‖	14 (7)	0.6	30 (16)	1.9	32 (17)	2.4
Gastrointestinal disorders						
Nausea	79 (41)	5.0	74 (39)	5.7	63 (34)	5.6
Diarrhea	70 (37)	4.4	26 (14)	1.5	63 (34)	5.9
Vomiting¶	57 (30)	3.1	52 (27)	3.4	29 (16)	2.1
Abdominal pain#	54 (28)	3.0	32 (17)	2.0	29 (16)	2.1
Constipation	42 (22)	2.1	27 (14)	1.6	12 (7)	0.8
Musculoskeletal and connective tissue disorders						
Arthralgia**	49 (26)	2.6	85 (44)	8.4	85 (46)	10.4
Myopathy††	45 (23)	2.2	64 (33)	5.0	41 (22)	3.3
Pain in extremity	21 (11)	1.0	42 (22)	2.8	25 (13)	1.9
Back pain	18 (9)	0.8	29 (15)	1.8	11 (6)	0.8
Skin and subcutaneous tissue disorders						
Hyperkeratosis‡‡	44 (23)	2.3	110 (57)	14.6	92 (50)	12.1
Rash§§	43 (22)	2.2	79 (41)	7.2	99 (53)	14.3
Dry skin‖‖	31 (16)	1.5	72 (38)	6.2	49 (26)	4.2
Alopecia¶¶	27 (14)	1.3	108 (56)	12.8	70 (38)	7.1
Pruritus##	24 (13)	1.1	59 (31)	4.6	39 (21)	3.4
PPE syndrome	13 (7)	0.6	98 (51)	9.8	26 (14)	1.9
Photosensitivity***	9 (5)	0.4	8 (4)	0.5	56 (30)	5.2
Nervous system disorders						
Headache†††	42 (22)	2.0	54 (28)	3.9	37 (20)	3.0
Dizziness‡‡‡	29 (15)	1.4	12 (6)	0.7	8 (4)	0.6
Neuropathy§§§	23 (12)	1.1	42 (22)	2.8	25 (13)	1.9
Eye disorders						
Visual impairment‖‖‖	39 (20)	2.1	11 (6)	0.6	8 (4)	0.5
Serous retinopathy¶¶¶	38 (20)	1.9	4 (2)	0.2	3 (2)	0.2
Vascular disorders						
Hemorrhage###	36 (19)	1.7	21 (11)	1.2	16 (9)	1.1
Hypertension****	22 (12)	1.0	11 (6)	0.6	21 (11)	1.5
Cardiac disorders						
Left ventricular dysfunction††††	15 (8)	0.7	4 (2)	0.2	1 (1)	0.1
Neoplasms benign, malignant and unspecified disorders (of the skin)						
Skin papilloma‡‡‡‡	14 (7)	0.6	20 (10)	1.2	36 (19)	2.9
CuSCC§§§‖	5 (3)	0.2	15 (8)	0.9	32 (17)	2.5
Basal cell carcinoma	3 (2)	0.1	2 (1)	0.1	3 (2)	0.2

AESI=adverse event of special interest; COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; CuSCC=cutaneous squamous cell carcinoma; EAIR=exposure-adjusted incidence rate; ENCO300=encorafenib 300 mg once daily; PPE=palmar-plantar erythrodysaesthesia; VEM=vemurafenib 960 mg twice daily.
*EAIR per 100 patient-months of exposure to study drug.
†Includes fatigue, asthenia.
‡Includes pyrexia, body temperature increased, hyperpyrexia, hyperthermia.
§Includes peripheral edema, local swelling, localized edema, edema, peripheral swelling.
‖Includes erythema, generalized erythema, plantar erythema.
¶Includes vomiting, retching.
#Includes abdominal pain, abdominal discomfort, upper abdominal pain, epigastric discomfort, gastrointestinal pain.
**Includes arthralgia, joint pain, joint swelling.
††Includes muscle spasms, muscular weakness, myalgia, myositis.
‡‡Includes hyperkeratosis, hyperkeratosis follicularis et parafollicularis, keratosis pilaris, lichenoid keratosis, palmoplantar keratoderma, parakeratosis, skin hypertrophy.
§§Includes rash, exfoliative rash, erythematous rash, follicular rash, generalized rash, macular rash, maculopapular rash, papular rash, pruritic rash, vesicular rash.
‖‖Includes dry skin, asteatosis, xerodermia, xerosis.
¶¶Includes alopecia, alopecia totalis, diffuse alopecia.
##Includes pruritus, generalized pruritus, genital pruritus.
***Includes photosensitivity reaction, solar dermatitis.
†††Includes headache, head discomfort, migraine.
‡‡‡Includes dizziness, balance disorder, vertigo.
§§§Includes peripheral neuropathy, peripheral sensory neuropathy, neuralgia, neuropathy peripheral, paresthesia, peripheral motor neuropathy, peripheral sensory neuropathy, polyneuropathy, sciatica, sensory disturbance, sensory loss.
‖‖‖Includes visual impairment, blurred vision, reduced visual acuity.
¶¶¶Includes retinal detachment, chorioretinopathy, cystoid macular edema, macular retinal pigment epithelium detachment, retinal pigment epithelium detachment, macular detachment, macular edema, metamorphopsia, retinal disorder, retinal exudates, retinal edema, retinal pigment epithelopathy, retinopathy, subretinal fluid.
###Includes rectal hemorrhage, hematochezia, hematuria, cerebral hemorrhage, epistaxis, hemorrhoidal hemorrhage, meningeal hemorrhage, metrorrhagia, retinal hemorrhage, subdural hematoma, vaginal hemorrhage, vaginal hemorrhage NOS, vaginal hemorrhage postmenopausal, vaginal spotting, vaginal ulcer hemorrhage, tumor hemorrhage, polymenorrhea, subdural hematoma, uterine hemorrhage, hemorrhagic diarrhea, hemoptysis, mucosal hemorrhage, occult blood, postprocedural hemorrhage, postmenopausal hemorrhage, pulmonary alveolar hemorrhage, tumor hemorrhage, vaginal hemorrhage, wound hemorrhage.
****Includes hypertension, essential hypertension, hypertensive crisis.
††††Includes ejection fraction decreased, cardiac failure, left ventricular dysfunction, and ejection fraction abnormal
‡‡‡‡Includes skin papilloma, papilloma, blepharal papilloma, oral papilloma.
§§§‖Includes keratoacanthoma, squamous cell carcinoma, lip squamous cell carcinoma, squamous cell carcinoma of skin.

Selected Adverse Events of Special Interest

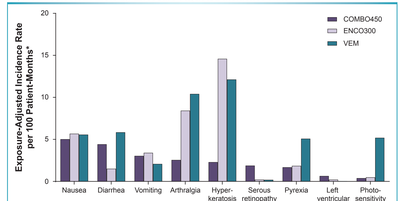
- The incidence of selected AESIs is presented in **Figure 2**. The exposure-adjusted incidence rates of these selected AESIs are presented in **Figure 3**.

Figure 2. Selected AESIs Occurring in Patients (All Grades) in Any Study Group



AESI=adverse event of special interest; COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; ENCO300=encorafenib 300 mg once daily; VEM=vemurafenib 960 mg twice daily.

Figure 3. Selected AESIs by Exposure-Adjusted Incidence Rate



AESI=adverse event of special interest; COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily; EAIR=exposure-adjusted incidence rate; ENCO300=encorafenib 300 mg once daily; VEM=vemurafenib 960 mg twice daily.
*EAIR per 100 patient-months=(n*100)/(total exposure time [in months]).

Pyrexia

- Rates of pyrexia were experienced by a lower proportion of patients in the COMBO450 (18%) and ENCO300 (16%) groups than in the VEM group (30%).
- In the COMBO450 group:
  - Most patients with an event experienced a maximum grade of grade 1 (23/35; 66%); no patients experienced a grade 4 event.
  - Pyrexia led to treatment discontinuation in 1% of patients (1/192) and dose interruption or adjustment in 4% (8/192).
  - Only 5% of patients (10/192) experienced more than 1 episode.
- For patients experiencing pyrexia, median times to first onset were:
  - COMBO450 group (n=33): 85 days (range, 2–545)
  - ENCO300 group (n=30): 2.5 days (range, 1–560)
  - VEM group (n=55): 19 days (range, 2–619)
- In a separate analysis, serious AEs (SAEs) of pyrexia (n=6) in the COMBO450 group were not associated with hypotension, chills/rigors, dehydration, renal failure, or syncope.
  - The majority of such events were associated with concurrent contributory factors such as disease progression or underlying infection.

Gastrointestinal AESIs of nausea, diarrhea, and vomiting

- Nausea was experienced by similar proportions of patients among the 3 treatment groups, occurring in 41%, 39%, and 34% of patients in the COMBO450, ENCO300, and VEM groups, respectively.
  - In the COMBO450 group, 25% of patients experienced a maximum grade of grade 1, 15% of grade 2, and 2% of grade 3.
- Diarrhea was experienced by similar proportions of patients in the COMBO450 and VEM groups (37% and 34%, respectively). These rates were higher than the rate observed in the ENCO300 group (14%).
  - In the COMBO450 group, 24% of patients experienced a maximum grade of grade 1, 10% of grade 2, 2% of grade 3, and 1% of grade 4.
- Vomiting occurred in 30% of patients in the COMBO450 group, in 27% in the ENCO300 group, and in 16% in the VEM group.
  - In the COMBO450 group, 18% of patients experienced a maximum grade of grade 1, 10% of grade 2, and 2% of grade 3.
- Discontinuations, dose modifications, and time to first onset for gastrointestinal (GI) AESIs in the COMBO450 group are described in **Table 3**.

Table 3. Characteristics of AESIs of Nausea, Diarrhea, and Vomiting in the COMBO450 Group

AESI	Discontinuation, %	Dose modification, %	Time to first onset, days (range)
Nausea	0	8	29 (1–614)
Diarrhea	1	4	29 (1–534)
Vomiting	0	7	57 (1–607)

AESI=adverse event of special interest; COMBO450=encorafenib 450 mg once daily plus binimetinib 45 mg twice daily.

Arthralgia

- A lower proportion of patients experienced arthralgia in the COMBO450 group (26%) than in the ENCO300 (44%) or VEM groups (46%).
- In the COMBO450 group:
  - Grade 1, grade 2, and grade 3 events were experienced by 19%, 6%, and 1% of patients, respectively.
  - Arthralgia did not result in study drug discontinuation; dose interruption or adjustment occurred in 2% of patients.
  - For patients experiencing arthralgia (n=45), the median time to first onset was 85 days (range, 1–708).

Hyperkeratosis

- A lower proportion of patients experienced hyperkeratosis in the COMBO450 group (23%) than in the ENCO300 (57%) or VEM group (49%).
- In the COMBO450 group:
  - Grade 1, grade 2, and grade 3 events were experienced by 17%, 5%, and 1% of patients, respectively.
  - Hyperkeratosis did not result in study drug discontinuation but led to dose interruption or dose adjustment in 2% of patients.
  - For patients experiencing hyperkeratosis (n=42), median time to first onset was 77 days (range, 1–408).

Photosensitivity

- Photosensitivity occurred in 5% of patients in the COMBO450 group, 4% in the ENCO300 group, and 30% in the VEM group.
- In the COMBO450 group:
  - All events were grade 1 or 2, with the exception of one grade 3 event.
  - Photosensitivity did not lead to study drug discontinuation; 1 patient (1%) had dose interruption/adjustment.
  - For patients experiencing photosensitivity (n=9), median time to first onset was 84 days (range, 1–677).

Serous retinopathy

- Serous retinopathy occurred in 20% of patients in the COMBO450 group, 2% in the ENCO300 group, and 2% in the VEM group.
- In the COMBO450 group:
  - Grade 1 (asymptomatic), grade 2, and grade 3 events were experienced by 12%, 5%, and 3% of patients, respectively.
  - None of these events led to study drug discontinuation; serous retinopathy led to dose interruption or modification in 6% of patients.
  - For patients experiencing serous retinopathy (n=38), the median time to first onset in patients was 38 days (range, 1–532).
  - Clinical review of serous retinopathy events indicated that these events were generally reversible. In patients who experienced a serous retinopathy event, 82% of events (31/38) were reported as "recovered" and 3% (1/38) as "recovering."

Left ventricular dysfunction

- Left ventricular dysfunction (LVD) was reported in a higher percentage of patients in the COMBO450 group (8%) compared with the ENCO300 (2%) and VEM groups (1%).
- In the COMBO450 group:
  - Grade 1, grade 2, and grade 3 events were experienced by 2%, 4%, and 2% of patients, respectively.
  - LVD did not result in study drug discontinuation; dose interruption or adjustment occurred 6% of patients.
  - Median time to first onset was 109 days (range, 1–648).
  - Clinical review of LVD events found that they were generally reversible upon dose reduction or discontinuation. In patients in whom LVD was reported, 93% of events (14/15) were reported as "recovered," of which 1 event was reported as "resolved with sequelae."

CONCLUSIONS

- Common BRAF/MEKi toxicities were generally manageable, reversible, and infrequently associated with treatment discontinuation with COMBO450.
  - No serious unexpected AESIs were observed.
- In patients treated with COMBO450, pyrexia was infrequent and was mainly associated with disease progression or underlying infection.
- Photosensitivity was infrequent in patients treated with COMBO450.
- Serous retinopathy was mainly asymptomatic (grade 1) or of low severity and reversible.
- LVD was often managed by dose interruption and reduction but was generally reversible and did not require treatment discontinuation.
- This analysis of AESIs suggests that COMBO450 is generally well tolerated with a differentiated safety profile in patients with *BRAF*^{V600}-mutant melanoma.

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CONFLICTS OF INTEREST

HJG has received consulting fees from Roche, Bristol-Myers Squibb, Merck Sharp & Dohme, Novartis, and Amgen, and research funding from Bristol-Myers Squibb, and Merck Sharp & Dohme outside the submitted work. RD has had intermittent, project-focused consulting or advisory roles on behalf of his institution, and honoraria, with Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Amgen, Takeda, and Pierre Fabre outside the submitted work. PAD received fees at the University of Zurich, which received research-funding from Roche, Novartis, research projects from Novartis, Merck Sharp & Dohme, Bristol-Myers Squibb, and Roche outside the submitted work. PAA has received consulting fees from Bristol-Myers Squibb, Roche Genentech, Merck Sharp & Dohme, Novartis, Amgen, Array BioPharma, Merck Serono, Pierre Fabre, Incyte, NewLink Genetics, Genmab, Medimmune, Syndax, and AstraZeneca. He has received research funding from Bristol-Myers Squibb, Roche Genentech, and Array BioPharma outside the submitted work. AA has received honoraria from, had a consulting or advisory role with, or been a member of the speakers bureau for Novartis, Roche, Merck Sharp & Dohme, and Bristol-Myers Squibb outside the submitted work, and has received travel expenses from Roche and Bristol-Myers Squibb. MM has received personal fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, Novartis, and Pierre Fabre outside the submitted work. GL has received consulting fees from Roche, Merck Sharp & Dohme, Bristol-Myers Squibb, and Novartis outside the submitted work. CG has received personal fees and research funding from Novartis and Pierre Fabre during the conduct of the study. He has received personal fees for presentations and consulting or advisory roles from Amgen, Bristol-Myers Squibb, Merck Sharp & Dohme, Philogen, and Roche and research funding from Bristol-Myers Squibb and Roche outside the submitted work. DS has received personal fees and patients' fees from Pierre Fabre during the conduct of the study. He has received honoraria and travel expenses from, has a consulting or advisory role, been a member of the speakers bureau, and received personal fees from Amgen, Boehringer Ingelheim, LEO Pharma, Roche, Merck Sharp & Dohme, Incyte, Regeneron, 4SC, AstraZeneca, Bristol-Myers Squibb, Pierre Fabre, Merck-EMD, Pfizer, Philogen, and Array BioPharma. He has received patients' fees from Roche, Merck Sharp & Dohme, Regeneron, Bristol-Myers Squibb, Merck-EMD, and Philogen outside the submitted work. IK is an advisory board member and has received travel expenses from Bristol- Myers Squibb, Novartis, and Merck Sharp & Dohme during the conduct of the study. RG has received personal fees from Novartis and Pierre Fabre, received patients' fees from Novartis and Array BioPharma, and research funding from Novartis during the conduct of the study. He has received honoraria for lectures and consulting fees from Roche, Bristol-Myers Squibb, Novartis, Almirall, LEO Pharma, Amgen, Incyte, Boehringer Ingelheim, Regeneron, 4SC, AstraZeneca, Merck-EMD, Philogen, Johnson & Johnson, and Pfizer. He has received research funding from Novartis, Pfizer, and Johnson & Johnson, non-financial support from Roche, and travel expenses from Bristol-Myers Squibb outside the submitted work. CR has received consulting fees from Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, and Pierre Fabre outside the submitted work. JWBdG reports personal fees from Roche, Bristol-Myers Squibb, and Merck Sharp & Dohme outside the submitted work. KF reports research funding from Bristol-Myers Squibb during the conduct of the study. He has received personal fees from Bristol-Myers Squibb and personal fees and research funding from Ono Pharmaceutical, Merck Sharp & Dohme, and Novartis outside the submitted work. CL reports personal fees from Roche, Novartis, Bristol-Myers Squibb, Merck Sharp & Dohme, Pierre Fabre, LEO Pharma, and Amgen outside the submitted work. MDP and AG were employees and shareholders of Array BioPharma during the conduct of the study. CR participated in advisory boards for Pierre Fabre, Roche, Novartis, Bristol-Myers Squibb, Merck, Array BioPharma, and Amgen outside the submitted work. KTF received consulting fees from Array BioPharma, Novartis, and Roche and received research funding from Novartis during the conduct of the study. CO and LAM-dP declare no competing interests.

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Acknowledgments

We thank the patients, their families, and the sites that participated in this study. For editorial support, funded by Array BioPharma, we thank Shelly Lim and Marianna Ovnic.

This study was sponsored by Array BioPharma, Inc., with funding support from Novartis Pharmaceuticals Corporation.

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