

**Treatment of Rheumatoid Arthritis with a MEK Inhibitor:
Results of a 12-Week, Randomized, Placebo-Controlled
Phase 2 Study in Patients with Active Rheumatoid Arthritis
on a Background of Methotrexate**

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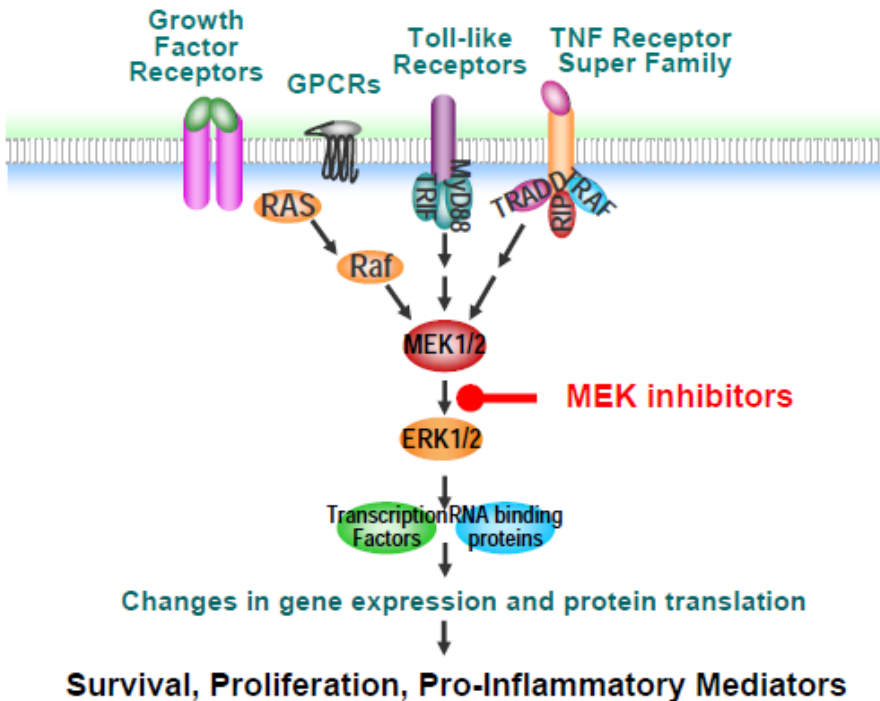
Disclosures

J. Kay, W. Maksymowych & M. Weisman:
Consultants for Array Biopharma, Inc.

A. Neitzel, A. James, S.G. Miller, J. Yates & S. Rojas-Caro:
Employees & Shareholders of Array Biopharma, Inc.

R. Morales, L. Bellatin, J. Brzezicki & P. Sirály:
None Declared

MEK/ERK Signaling Pathway in Inflammation



MEK (MAPK/ERK kinase) is a potential target in inflammation:

- MEK is a key kinase involved in mediating and propagating the effects of pro-inflammatory cytokines: TNF α , IL-1 β and IL-6.
- Protein therapeutics targeted against TNF α , IL-1 β and IL-6 are approved for treatment of RA.
- MEK inhibitors have demonstrated efficacy in animal models of rheumatoid arthritis.
- MEK inhibitors block osteoclast differentiation and function *in vitro*.

ARRY-162

- Potent small molecule inhibitor of MEK1/2
 - IC₅₀ 12 nM in enzymatic assays
 - IC₅₀ 5 nM in cellular assays
- Highly selective compared to other kinase inhibitors
 - Unique binding site; ARRY-162 does not compete with ATP binding
 - No inhibition >30% of other than MEK1 at 1 μM in a panel of 220 other kinases
- Oral efficacy in acute and sub-chronic animal models of joint inflammation
 - Carageenan-induced paw edema
 - Collagen-induced arthritis & adjuvant-induced arthritis
- Pharmacokinetics, pharmacodynamics, and safety profile established in Phase I clinical studies
 - Single-ascending dose and 14-day multiple ascending dose in healthy volunteers
 - 29-day study in RA patients on a stable MTX dose

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Study Design

- 12-week, Phase 2, randomized, double-blind, placebo-controlled multicenter study
- Study Aims: Investigate the safety, pharmacokinetics, and efficacy of ARRY-162, administered orally daily in patients with active RA incompletely responsive to methotrexate
- Study Population:
 - 201 patients randomized (1:1:1:1)
- Four treatment arms
 - ARRY-162 10 mg BID
 - ARRY-162 20 mg BID
 - ARRY-162 40 mg QD
 - Placebo
- Primary Endpoint: ACR20 response at week 12

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Study Design

- Key Secondary Endpoints

- Efficacy

- ACR20/50/70 response at Baseline & Weeks 1, 2, 4, 8, 12 & 16
- Components of ACR score at Baseline & Weeks 1, 2, 4, 8, 12 & 16
- DAS28-4[CRP] at Baseline & Weeks 1, 2, 4, 8, 12 & 16
- SF-36 Health Questionnaire (v. 2) at Baseline & Weeks 4, 8, 12 & 16
- Overall incidence & time to withdrawal due to lack of efficacy

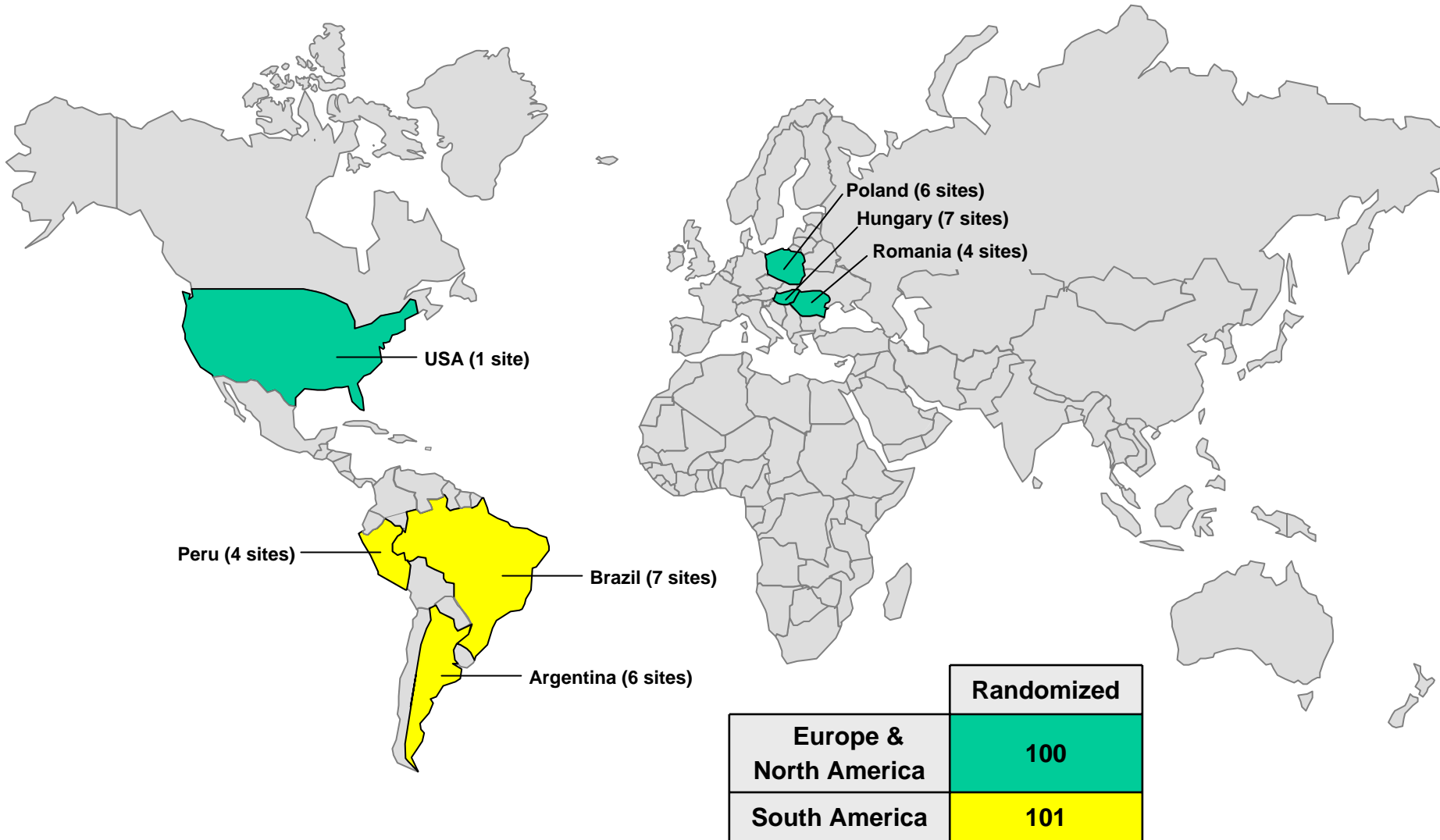
- Safety

- Incidence and severity of AEs
- Change from baseline in physical examination, clinical chemistries, vital signs, 12-lead ECG parameters

- Pharmacokinetics

- Plasma concentrations of ARRY-162 and a metabolite

ARRY-162-201 Clinical Sites



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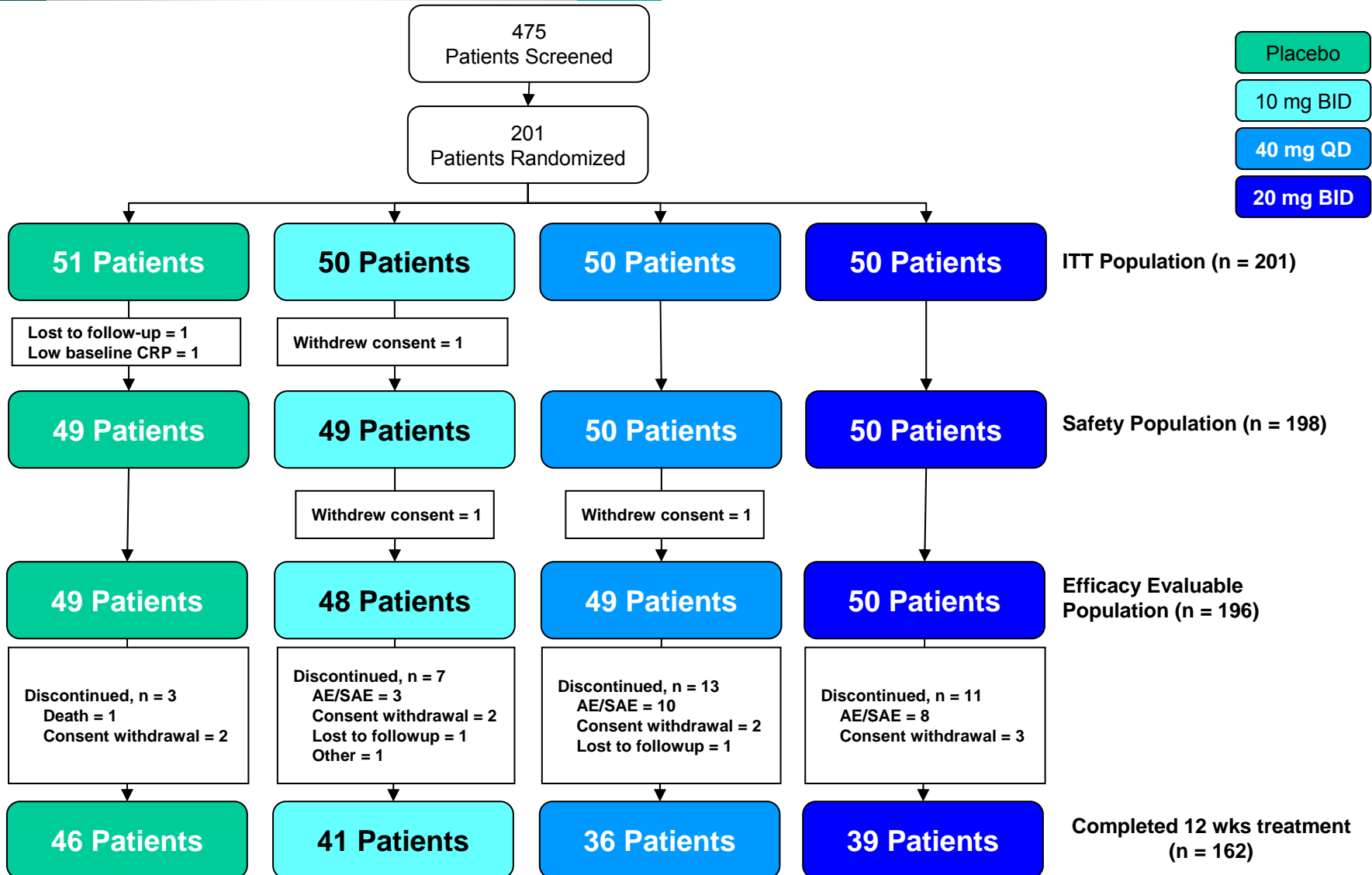
Key Eligibility Criteria

- ≥18 years of age
- RA diagnosed by ACR 1987 Revised Criteria
- Incompletely responsive to MTX:
 - ≥6 tender joints (28-joint count)
 - ≥6 swollen joints (28-joint count)
 - CRP ≥ 10 mg/L
- Stable methotrexate dose (10-25 mg weekly) for ≥ 6 weeks prior to screening
- No prior biological agents to treat RA

- 4-week washout period, if on a DMARD in addition to MTX
- Could continue on stable background therapy for RA
 - NSAIDs, opioid analgesics, acetaminophen, aspirin, antimalarials
 - prednisone ≤10 mg/day (or equivalent)

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Patient Disposition



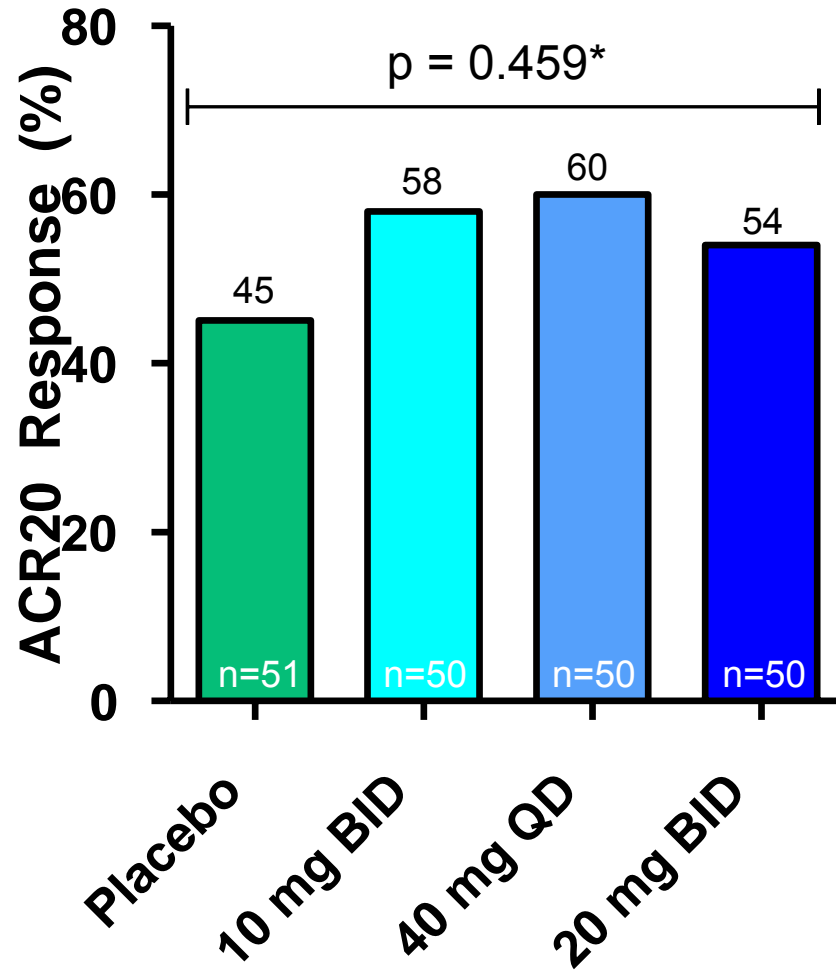
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Baseline Demographic Characteristics

Factor	Placebo	10 mg BID	40 mg QD	20 mg BID
Female (%)	84	84	86	88
Caucasian (%)	73	76	74	64
Mean age (yr)	52	52	55	51
Mean weight (kg)	74	68	72	67
Mean duration of RA (months)	89.6	93.4	88.6	95.7
RF+ / anti-CCP+ (%)	78 / 86	88 / 90	84 / 90	92 / 90
Never smoked nicotine (%)	75	78	72	72
Mean MTX dose (mg/week)	14.4	13.2	14.5	14.0
Mean duration of MTX (months)	16.3	21.8	18.6	16.1
Mean HAQ	1.6	1.5	1.5	1.5
Mean screening CRP (mg/L)	32	33	31	31
Mean baseline CRP (mg/L)	19	18	24	24

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Primary Efficacy Endpoint: ACR20 at 12 Weeks



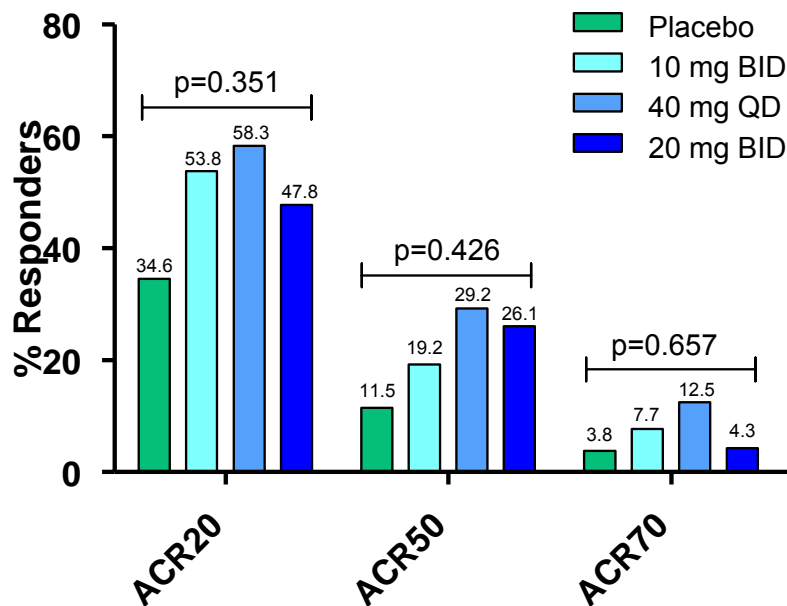
ACR20 at 12 weeks using last observation carried forward (LOCF), based on the intention-to treat (ITT) population
*Global Chi-square test

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12-wk response rates using LOCF based on EE population

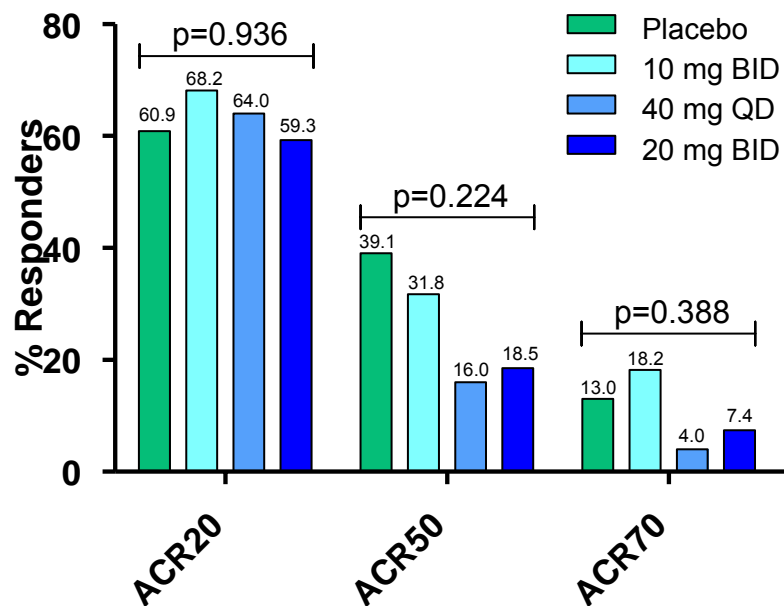
Europe / North America

Week12 ACR Response Rates
Europe/NA, EE, LOCF



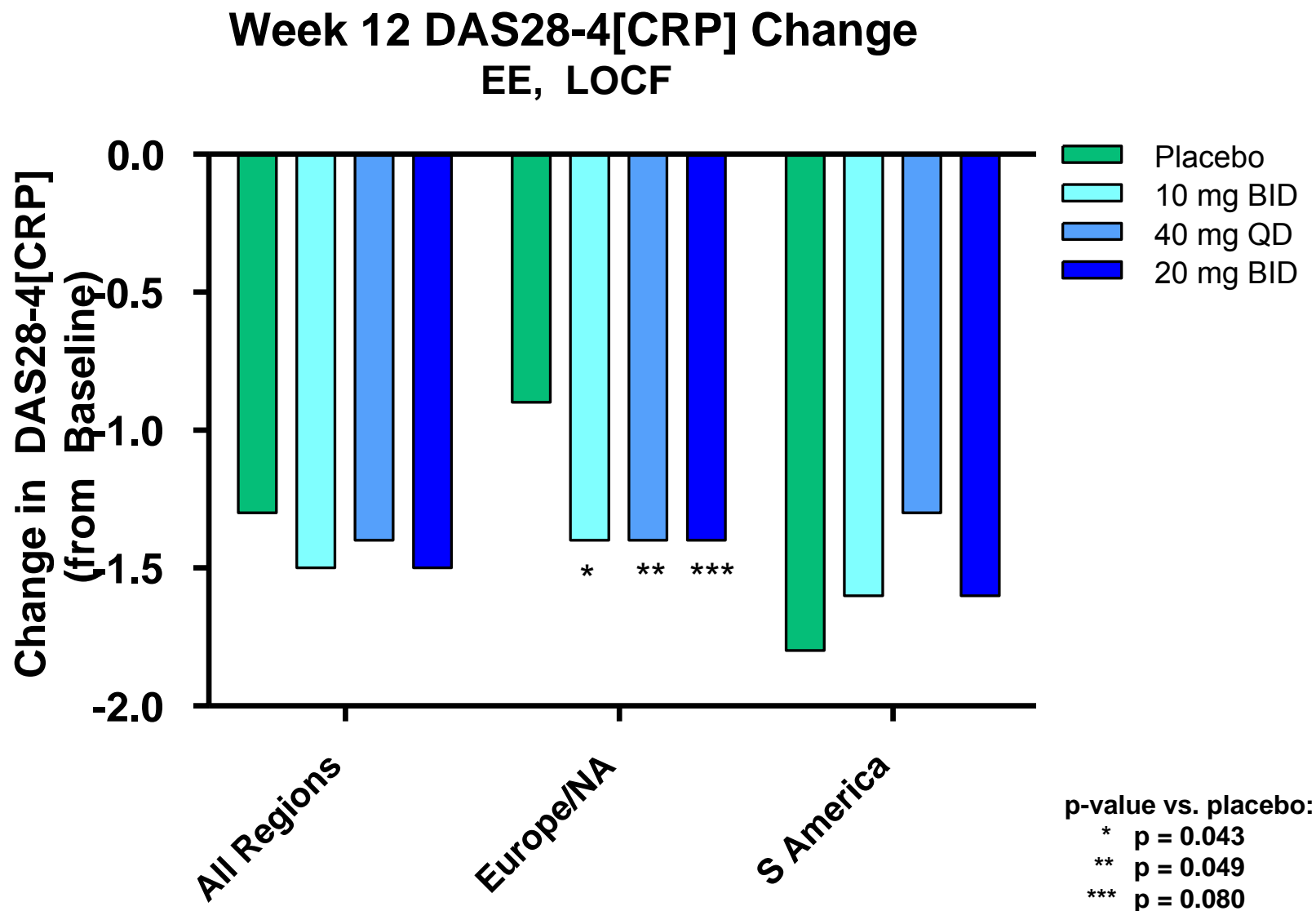
South America

Week12 ACR Response Rates
South America, EE, LOCF



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12-wk DAS28-4[CRP] using LOCF based on EE population



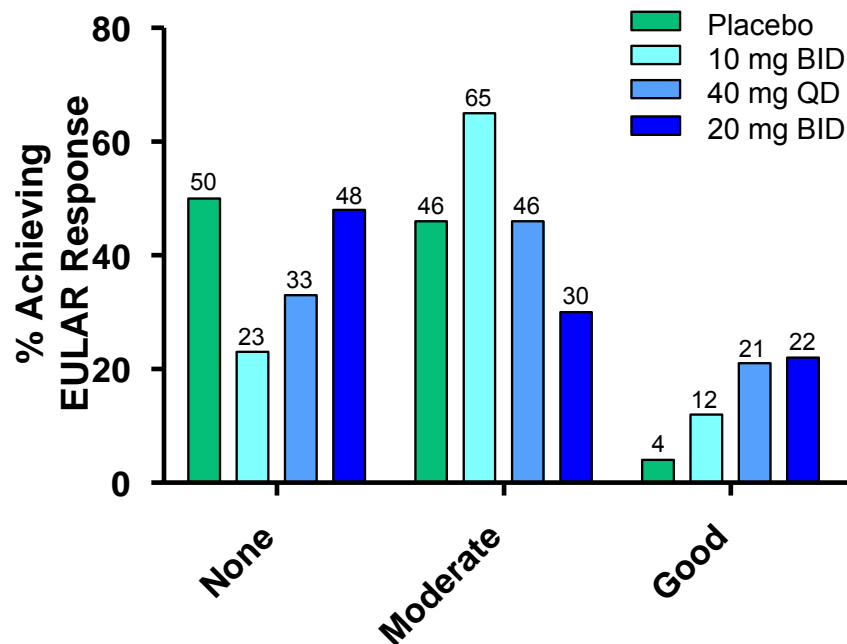
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12-wk EULAR Response using LOCF based on EE population

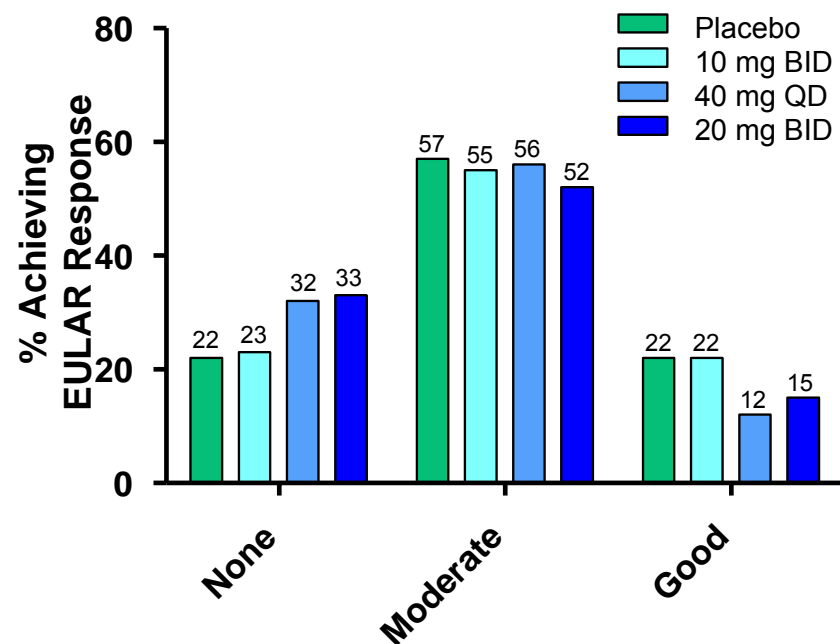
Europe / North America

South America

Week 12 EULAR Response
Europe/NA, EE, LOCF



Week 12 EULAR Response
South America, EE, LOCF



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Safety Population

- 198 patients who received study drug
- 21 patients discontinued the study due to an AE:
 - Placebo: 0/49 (0%)
 - 10 mg BID: 3/49 (6%)
 - 40 mg QD: 10/50 (20%)
 - 20 mg BID: 8/50 (16%)
 - $P < 0.001$
- Mean number of days of exposure to study drug:
 - Placebo: 81.4 days
 - 10 mg BID: 78.8 days
 - 40 mg QD: 68.4 days
 - 20 mg BID: 73.0 days
 - $P = 0.026$

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Most Commonly Reported Treatment-Emergent AEs

By Treatment Group

MedDRA Preferred Term	Placebo N=49	10 mg BID N=49	40 mg QD N=50	20 mg BID N=50
Rash*	4%	20%	30%	44%
Diarrhea	10%	6%	30%	24%
Nausea	0	0	12%	4%
Peripheral Edema	2%	2%	6%	6%
Abnormal Liver Function Tests**	6%	2%	6%	8%
Urinary Tract Infection	8%	8%	4%	10%
Bronchitis	4%	4%	2%	8%

*includes events of rash, rash pustular, rash erytematous, rash papular, folliculitis, acne, dermatitis acneiform, eczema, prurigo, rosacea, urticaria, and erythema

** includes events of alanine aminotransferase increased, aspartate aminotransferase increased, gama-glutamyltransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased

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Severity of Commonly Reported Treatment-Emergent AEs

All ARRY-162 Dose Levels, by Severity (N=149)

MedDRA Preferred Term	Grade 1	Grade 2	Grade 3
Rash*	18%	12%	1%
Diarrhea	16%	3%	1%
Nausea	4%	1%	0
Peripheral Edema	7%	0	0
Abnormal Liver Function Tests**	5%	0	0
Urinary Tract Infection	5%	2%	<1%
Bronchitis	1%	3%	0

*includes events of rash, rash pustular, rash erytematous, rash papular, folliculitis, acne, dermatitis acneiform, eczema, prurigo, rosacea, urticaria, and erythema

** includes events of alanine aminotransferase increased, aspartate aminotransferase increased, gama-glutamyltransferase increased, hepatic enzyme increased, liver function test abnormal, and transaminases increased

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Study Discontinuations Due to AEs by Region

Region	Placebo N=49	10 mg BID N=49	40 mg QD N=50	20 mg BID N=50	Total Treated N=149
E. Europe/ N. America	0	4%	8%	9%	7%
South America	0	9%	31%	22%	21%

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Summary

- In this study, ARRY-162 administered over 12 weeks was not effective in treating the signs and symptoms of active RA in patients with an incomplete response to methotrexate.
 - High placebo response rate in South America vs. Eastern Europe / North America may have limited the ability to detect a significant difference in efficacy between placebo and study drug
 - In the Eastern European / North American region, but not in South America, modest trends toward efficacy vs. placebo, based upon:
 - ACR20 response at Week 12
 - Change in DAS28-4[CRP] from Baseline
 - “Good” EULAR response at Week 12
- Most common AEs on study drug were mild to moderate skin-related disorders & diarrhea
- No SAEs related to study drug

Backup Slide

ARRY-162-201: Mean CRP Over Time

