P081

Evobrutinib efficacy is maintained over two years in an open-label Phase II study extension in patients with relapsing multiple sclerosis

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CONCLUSION

- **With evobrutinib 75 mg BID, the efficacy observed at Week 48 (ARR, 0.11) was maintained at 108 weeks (ARR, 0.12)**
- **Probability of and time to QR highlighted that, despite switching to evobrutinib 75 mg QD/BID in the OLE, patients treated with evobrutinib 25 mg QD, 75 mg QD or placebo in the DBP did not achieve the same level of efficacy as those initiated on 75 mg BID**
- **The maximum efficacy observed at the 75 mg BID dose correlated with optimal BTK occupancy of >95% in 98% of patients achieved with BID dosing**
- **These long-term efficacy data in patients with relapsing MS are the first to be reported for the class of agents that inhibit BTK**

ARR, annualized relapse rate; **BID,** twice daily; **BTK,** Bruton's tyrosine kinase; **DBP,** double-blind period; **MS,** multiple sclerosis; **OLE,** open-label extension; **QD,** once daily; **QR,** qualified relapse

INTRODUCTION

- Evobrutinib is a highly selective BTKi with a dual mode of action targeting both B cells and myeloid cells, which are known to play a key role in the pathogenesis of autoimmune diseases such as MS[1,2]
- Clinical efficacy of evobrutinib in relapsing MS was shown in a Phase II randomized controlled trial (NCT02975349) with a significant reduction of T1 Gd-enhancing lesions compared with placebo at Week 24 (the primary endpoint of the study) and continued efficacy through Week 48[3]

BTKi, Bruton's tyrosine kinase inhibitor

OBJECTIVE

To report the long-term efficacy of evobrutinib measured as:

ARR
Annualized Relapse Rate

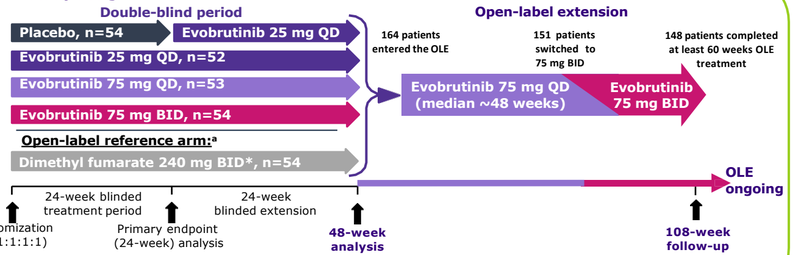
QR*
Cumulative probability of and time to qualified relapse

*QR defined as a change in neurological symptoms or Expanded Disability Status Scale score increase attributed to MS lasting ≥24 hours preceded by a stable or improving neurological status ≥30 days

METHODS

- In the 48-week DBP, patients received evobrutinib 25 mg QD, 75 mg QD, 75 mg BID or placebo for the first 24 weeks; all arms continued with the original treatment assignment until 48 weeks, except placebo patients who were switched to evobrutinib 25 mg QD
- At Week 48, all patients could enter the OLE, where treatment was initially evobrutinib 75 mg QD (for a median of ≈48 weeks) before switching to 75 mg BID. Here, efficacy of evobrutinib was assessed when all patients had completed at least 60 weeks of the ongoing OLE or discontinued

Figure 1. Study design



[a]Only patients treated with evobrutinib are included in the current analysis; *120 mg BID for the first 7 days, followed by 240 mg BID for the duration of treatment; **BID,** twice daily; **DBP,** double-blind period; **OLE,** open-label extension; **QD,** once daily

RESULTS

Evobrutinib BTK occupancy is highly correlated with efficacy

- BTK occupancy increased in a dose-dependent manner based on pre-dose (steady state trough) observations at Weeks 4, 12 and 24 (Table 1)
- The highest pre-dose BTK occupancy was observed with the 75 mg BID dose
- Lower trough occupancy observed at 25 and 75 mg QD doses resulted in no efficacy (25 mg) or lower efficacy (75 mg) than 75 mg BID (Supplementary Table 1)
  - No efficacy for 25 mg QD despite 51% of trough samples >90% BTK occupancy

- **The largest and most sustained reduction in ARR was achieved when BTK occupancy was >95%, observed in nearly all patients receiving 75 mg BID (Table 1)**
- **95% BTK occupancy is necessary to reach maximum efficacy**

Table 1. BTK occupancy according to evobrutinib dose

BTK occupancy threshold	25 mg QD	75 mg QD	75 mg BID
	% of population*		
0.90	51	87	100
0.95	23	48	98

No efficacy → Maximum efficacy

*Based on 124 (35/46/43) pre-dose observations from 11–17 fasted patients per dose level at Weeks 4, 12, 24
BID, twice daily; **BTK,** Bruton's tyrosine kinase; **QD,** once daily

Patient disposition

- Of 213 patients randomized to evobrutinib or placebo, 164 (77%) entered the OLE; of these 148 (90%) completed at least 108 weeks of treatment (Table 2)

Table 2. Patients entering the OLE

Patients, n (%)	Placebo + evobrutinib 25 mg QD	Evobrutinib 25 mg QD	Evobrutinib 75 mg QD	Evobrutinib 75 mg BID
Entered OLE period	39 (72.2)	39 (75.0)	42 (79.2)	44 (81.5)
Switched to 75 mg BID during OLE	35 (64.8)	35 (67.3)	37 (69.8)	44 (81.5)
Discontinued treatment during OLE	5 (9.3)	9 (17.3)	5 (9.4)	3 (5.6)

BID, twice daily; **OLE,** open-label extension; **QD,** once daily

ARR maintained with long-term treatment

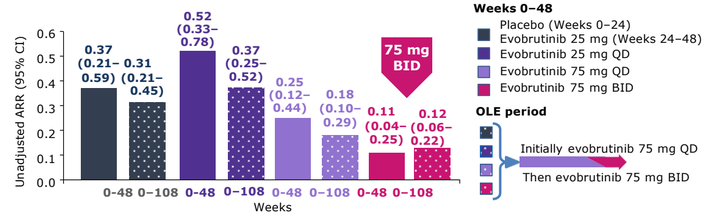
- In patients receiving evobrutinib 75 mg BID in the DBP, the efficacy at Week 48 (ARR, 0.11) was maintained at 108 weeks (ARR, 0.12, Figure 2)
- Patients starting on evobrutinib 75 mg BID in the DBP had a lower ARR compared with those starting on 75 mg QD, 25 mg QD or placebo in the DBP (Figure 2)

Table 3. Estimated time from randomization by which 20% of patients had a QR

Treatment	Time, weeks (95% CI)
Placebo/evobrutinib 25 mg QD	40.1 (14.1; 58.3)
Evobrutinib 25 mg QD	23.7 (8.7; 86.6)
Evobrutinib 75 mg QD	75.7 (34.9; 119.7)
Evobrutinib 75 mg BID	118.1 (46.7; NE)

BID, twice daily; **CI,** confidence interval; **NE,** not estimable; **QD,** once daily; **QR,** qualified relapse

Figure 2. Annualized relapse rate



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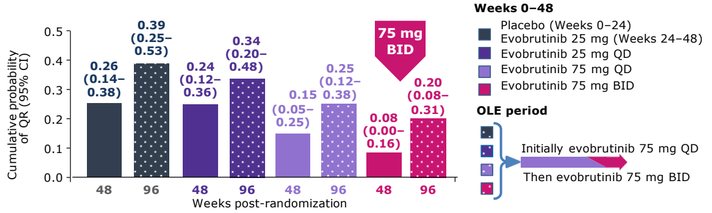
Lower probability of first QR with evobrutinib 75 mg BID

- Patients receiving evobrutinib 75 mg BID in the DBP had a lower cumulative probability of first QR after 48 weeks (QR, 0.08) and 96 weeks (QR, 0.20) compared with those receiving evobrutinib 75 mg QD, 25 mg QD or placebo in the DBP (Figure 3)

Figure 3. Cumulative probability of first QR*

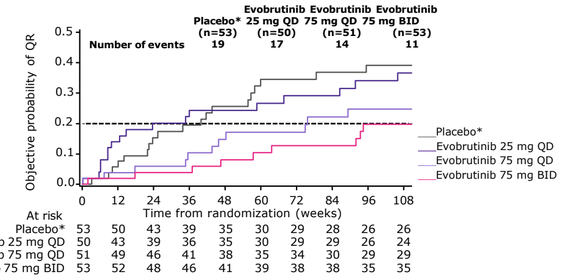


*Kaplan-Meier estimate
BID, twice daily; **CI,** confidence interval; **OLE,** open-label extension; **QD,** once daily; **QR,** qualified relapse

Estimated time from randomization to first QR

- The estimated time from randomization by which 20% of patients had a QR was (Figure 4, Table 3):
  - Three times longer for those treated with evobrutinib 75 mg BID in the DBP than for those who received placebo
  - Longer for those treated with evobrutinib 75 mg BID than with evobrutinib 25 mg QD or 75 mg QD

Figure 4. Estimated time from randomization to QR



At risk										
Placebo*	53	50	43	39	35	30	29	28	26	26
Evobrutinib 25 mg QD	50	43	39	36	35	30	29	29	26	24
Evobrutinib 75 mg QD	51	49	46	41	38	35	34	30	29	29
Evobrutinib 75 mg BID	53	52	48	46	41	39	38	38	35	35

*Patients switched from placebo to evobrutinib 25 mg QD for the second 24-week treatment period
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1. Hendriks RW. *Nat Chem Biol*. 2011;7:4–5; 2. Alankus YB, et al. Poster presented at ECTRIMS 2018 (P557); 3. Montalban X, et al. *N Engl J Med*. 2019;380:2406-2417.

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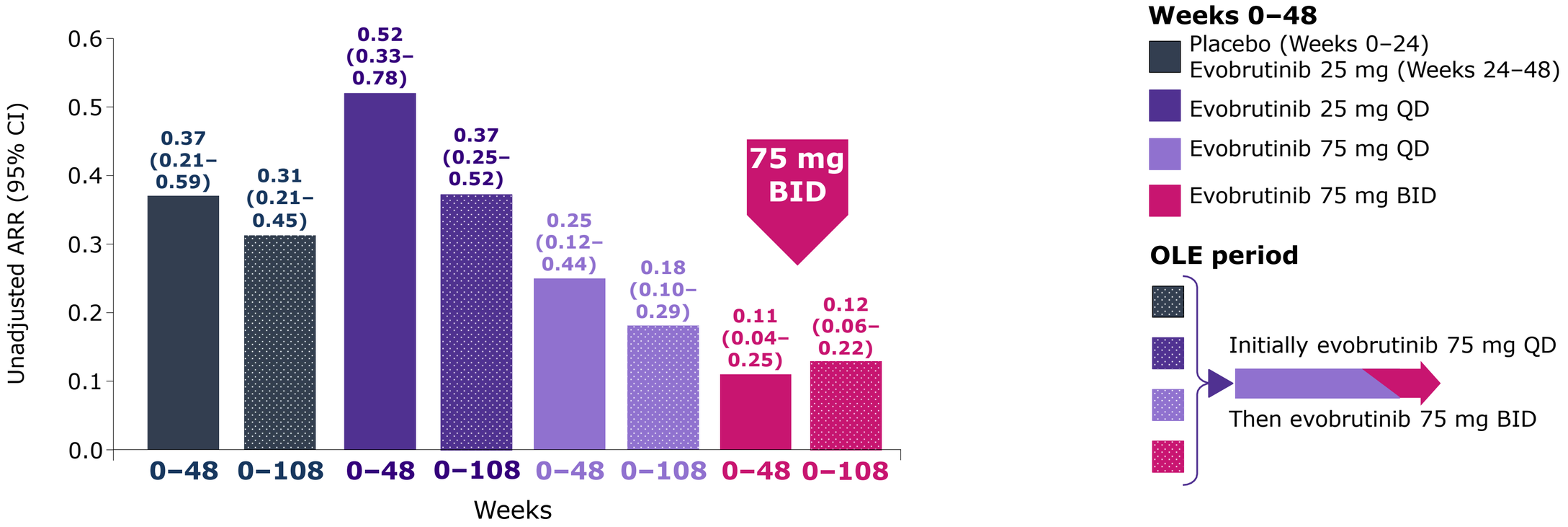

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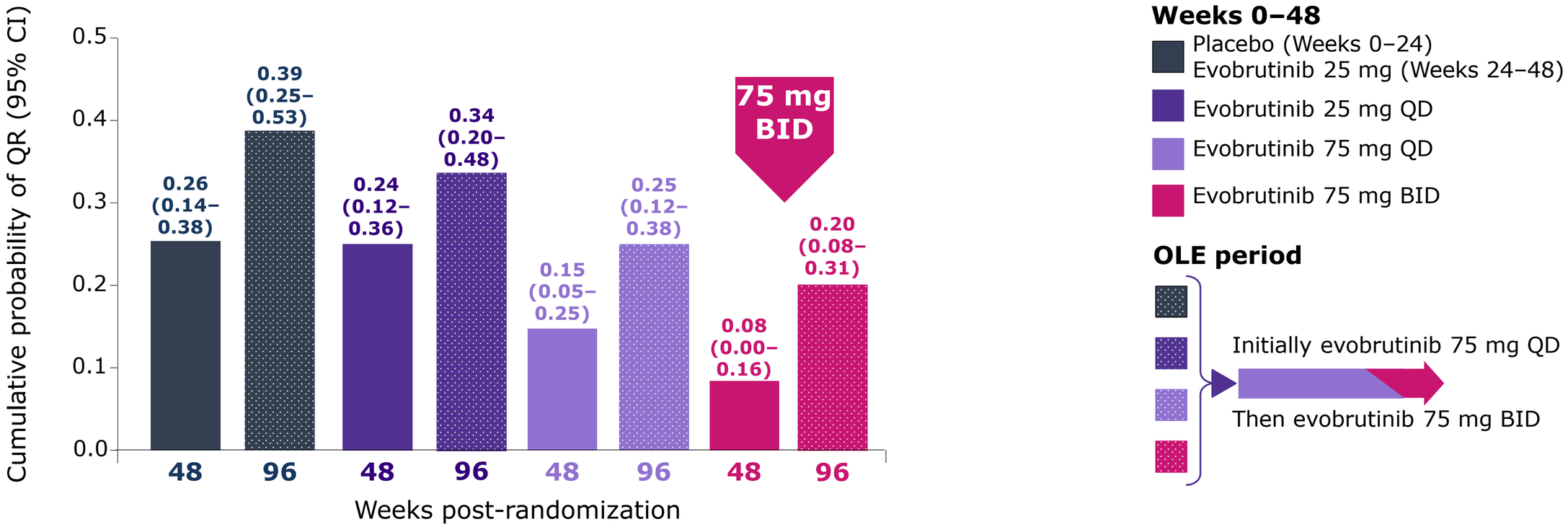

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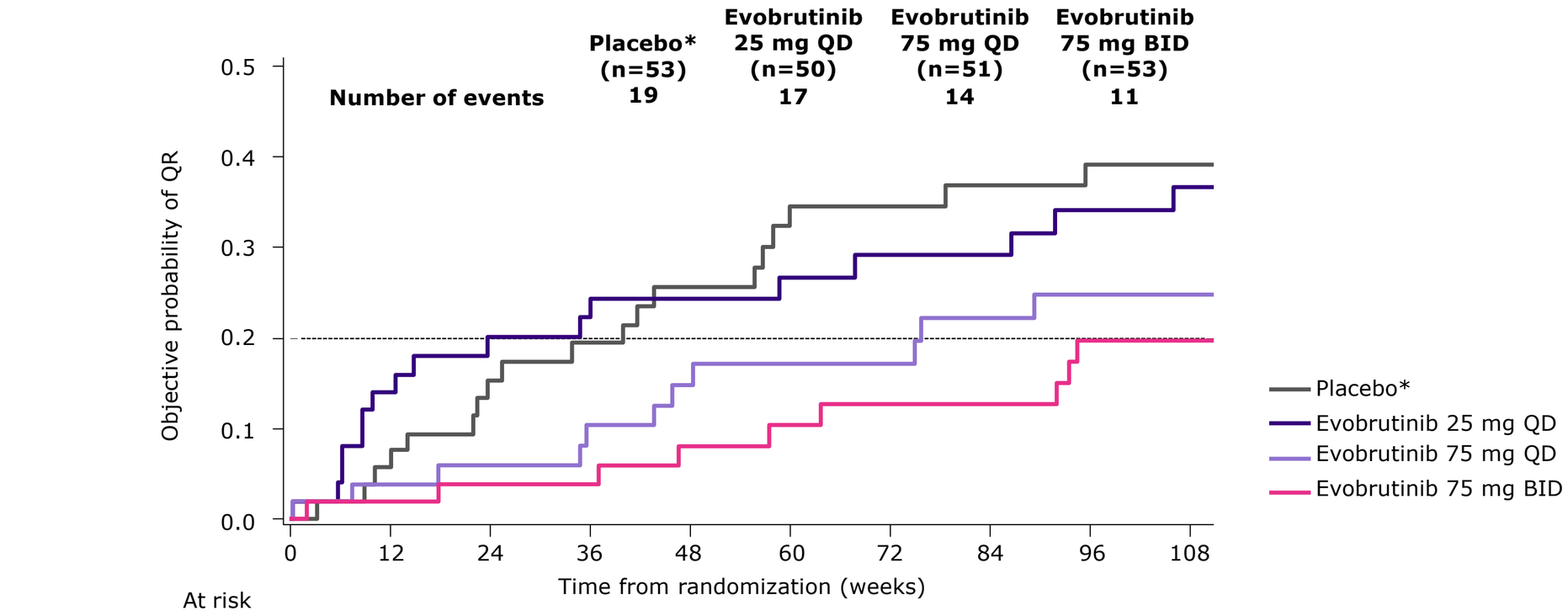

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Supplementary Table 1. BTK occupancy according to evobrutinib dose

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	% of population*		
0.70	91	100	100
0.80	80	98	100
0.90	51	87	100
0.95	23	48	98

*Based on 124 (35/46/43) pre-dose observations from 11–17 fasted patients per dose level at Weeks 4, 12, 24
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