European Crohn's and Colitis Organisation

Biomarker and pharmacokinetic data from the TURANDOT II open-label extension study of the anti-mucosal addressin cell adhesion molecule-1 (MAdCAM-1) antibody ontamalimab (SHP647) in patients with ulcerative colitis

Reinisch W,[1] *Sandborn WJ, Danese S, Hébuterne X, Kłopocka M, Tarabar D, Vaňásek T, Greguš M, Hellstern PA, Kim JS, Sparrow M, Gorelick KJ, Goetsch M, Bliss C, Gupta C, Cataldi F, Vermeire S*

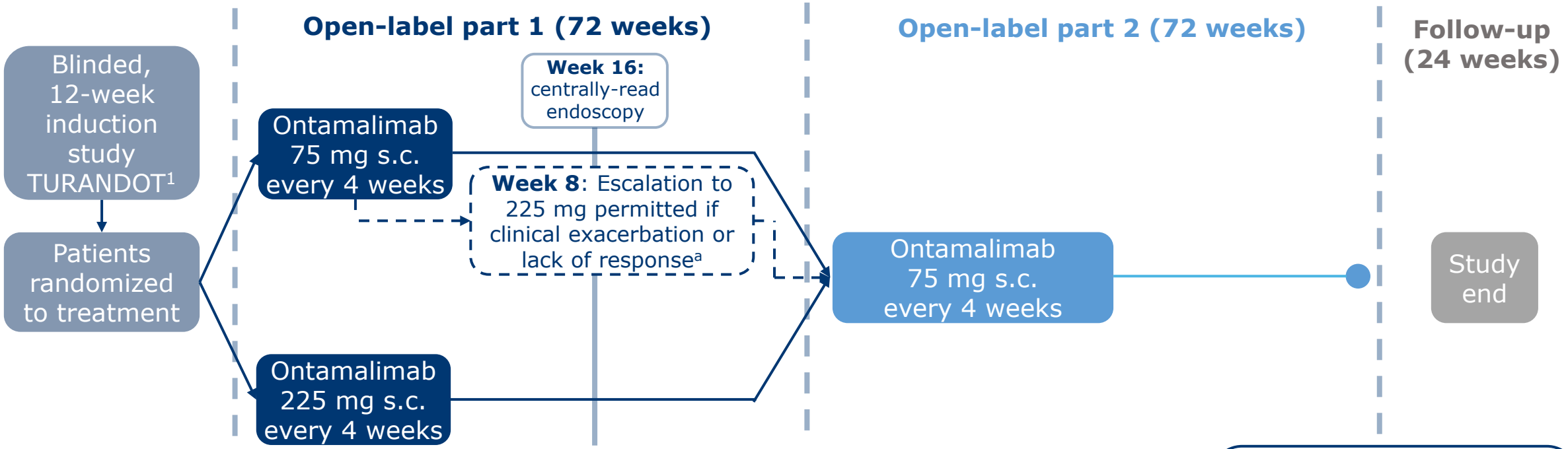
[1]*Medical University of Vienna, Vienna, Austria*

14th Congress of ECCO, Copenhagen, Denmark, 8 March 2019

Disclosures

I have received financial support for research from Abbott Laboratories, AbbVie, AESCA, Centocor, Dr. Falk Pharma GmbH, Immundiagnostik and Merck Sharp & Dohme; I have been a speaker for Abbott Laboratories, AbbVie, AESCA, Aptalis, Astellas, Celltrion, Centocor, Danone Austria, Elan, Dr. Falk Pharma GmbH, Ferring, Immundiagnostik, Merck Sharp & Dohme, Mitsubishi Tanabe Pharma Corporation, Otsuka, PDL BioPharma, Pharmacosmos, PLS Education, ScheringPlough, Shire (a member of the Takeda group of companies), Takeda, Therakos, Vifor and Yakult; been a consultant for 4SC, Abbott Laboratories, AbbVie, AESCA, Amgen, AM Pharma, AOP Orphan, Astellas, AstraZeneca, Avaxia, BioClinica, Biogen Idec, Boehringer Ingelheim, BristolMyers Squibb, Celgene, Cellerix, Celltrion, Centocor, ChemoCentryx, Covance, Danone Austria, Elan, Ernest & Young, Dr. Falk Pharma GmbH, Ferring, Galapagos NV, Genentech, Gilead, Grünenthal, ICON, InDex Pharmaceuticals, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin, Lipid Therapeutics GmbH, LivaNova, Mallinckrodt, MedImmune, Merck Sharp & Dohme, Millennium, Mitsubishi Tanabe Pharma Corporation, Nestlé, Novartis, Ocera Therapeutics, Otsuka, Parexel, PDL BioPharma, Pfizer, Pharmacosmos, Philip Morris International, Procter & Gamble, Prometheus, Provention Bio, Robarts Clinical Trials, Roland Berger GmBH, Sandoz, ScheringPlough, Second Genome, Seres Therapeutics, SetPoint Medical, Sigmoid, Takeda, Therakos, TiGenix, UCB, Vifor Pharma, Zealand and Zyngenil; acted as an advisory board member for 4SC, Abbott Laboratories, AbbVie, AESCA, Amgen, AMPharma, Astellas, AstraZeneca, Avaxia Biologics, Biogen Idec, Boehringer Ingelheim, BristolMyers Squibb, Celgene, Cellerix, Celltrion, Centocor ChemoCentryx, Danone Austria, Elan, Ferring, Galapagos NV, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin, Lipid Therapeutics GmbH, MedImmune, Merck Sharp & Dohme, Millennium, Mitsubishi Tanabe Pharma Corporation, Nestlé, Novartis, Ocera Therapeutics, Otsuka, PDL BioPharma, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, ScheringPlough, Second Genome, SetPoint Medical, Takeda, Therakos, TiGenix, UCB, Zealand and Zyngenia

TURANDOT II (NCT01771809): a phase 2, multicenter, two-part, open-label extension study in patients with UC



- Primary endpoints: safety and tolerability of ontamalimab
- Secondary endpoints: mucosal healing, ontamalimab pharmacokinetics and immunogenicity
  - Serum ontamalimab concentrations, measured every 4 weeks to week 72 and at 3-month follow up
- Exploratory endpoints: ontamalimab pharmacodynamics, durability of response and remission
  - Concentrations of hsCRP and FC, measured every 4 weeks to week 24, then at weeks 32 and 72
  - Soluble MAdCAM-1 concentrations, measured at weeks 0 and 16

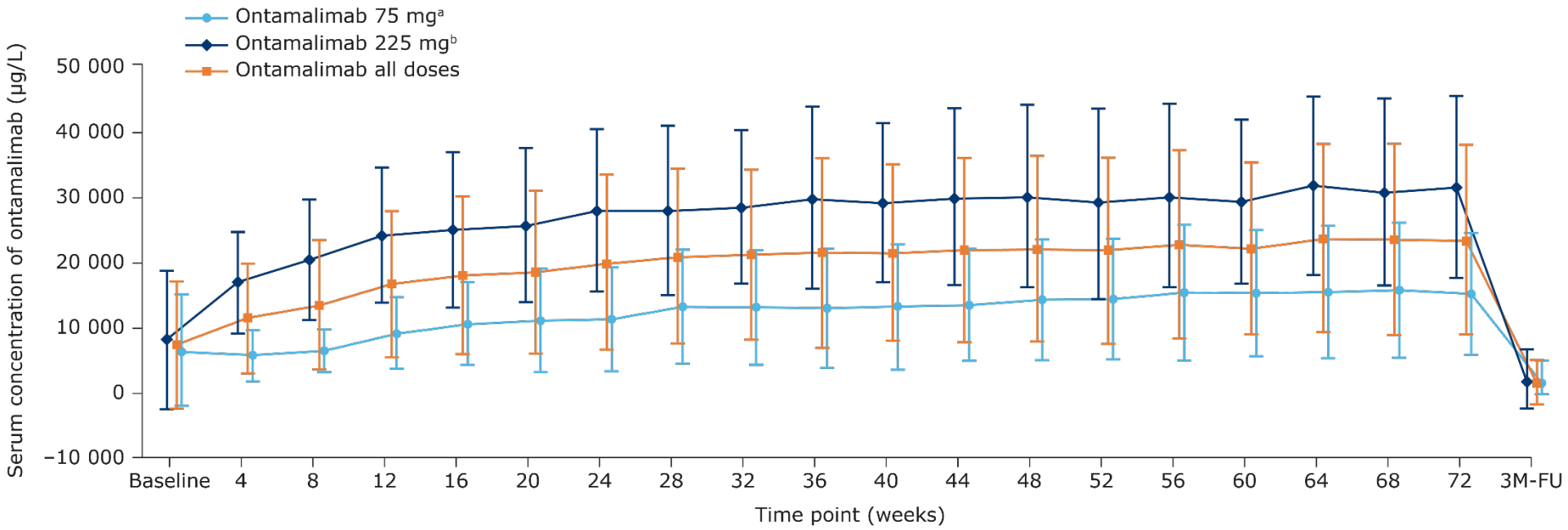
Clinical exacerbation
An increase in total Mayo score to > 6 or a partial Mayo score > 4, and one or both of the below:
- increase in rectal bleeding subscore to ≥ 2
- increase in stool frequency subscore to ≥ 2

[a]At investigator's discretion any time between week 8 and 72. FC, faecal calprotectin; hsCRP, high-sensitivity C-reactive protein; MAdCAM-1, mucosal addressin cell adhesion molecule-1; s.c., subcutaneously; UC, ulcerative colitis

1. Vermeire S *et al. Lancet* 2017;390:135–44

Mean (SD) serum concentrations of ontamalimab

Increased dose-dependently; PK steady state achieved at approximately week 12

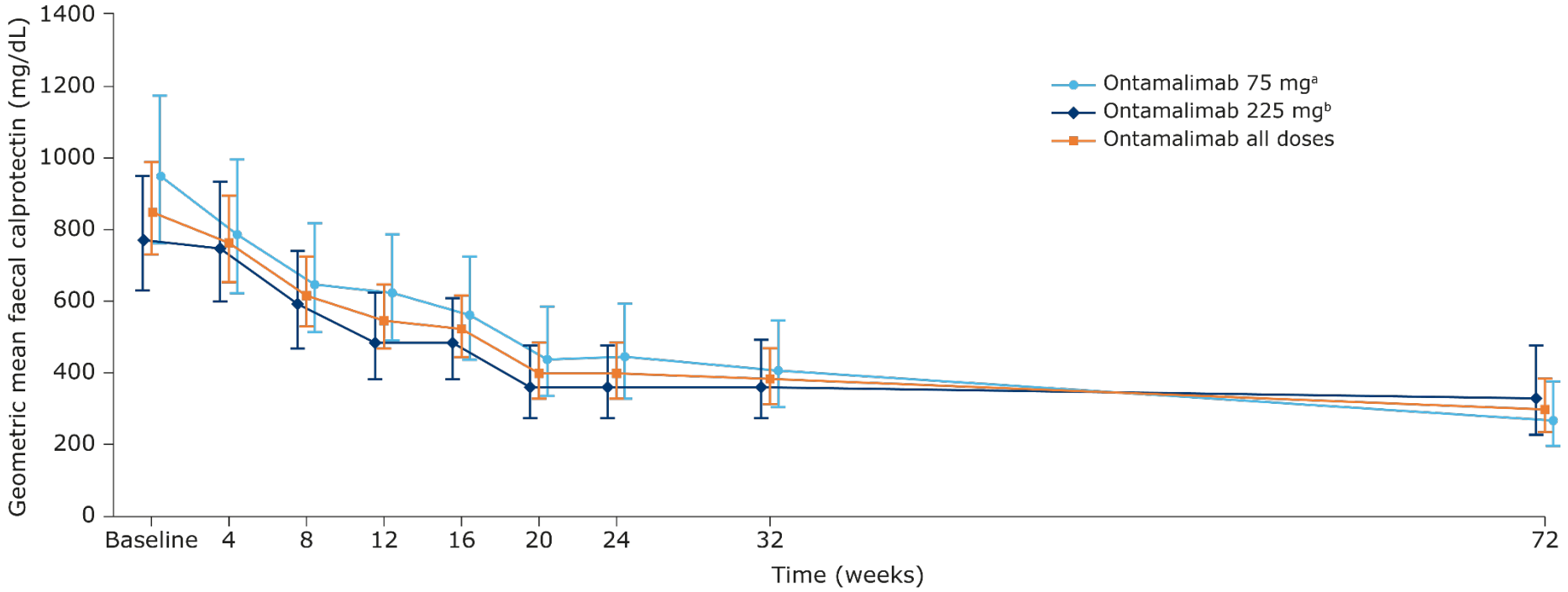


	Baseline	4	8	12	16	20	24	28	32	36	40	44	48	52	56	60	64	68	72	3M-FU
75 mg[b]	113	156	155	157	141	124	115	111	110	110	102	100	104	99	98	96	91	89	88	79
225 mg[c]	117	160	157	155	149	124	123	121	119	110	109	102	99	98	97	90	91	96	90	81
All doses	230	316	312	312	290	248	238	232	229	220	211	202	203	197	195	186	182	185	178	160

Patients included those who previously received ontamalimab and those who received placebo in TURANDOT; this is therefore reflected in ontamalimab concentrations at baseline (week 12 of TURANDOT).
Overall, 3/330 patients (one receiving 75 mg and two receiving 225 mg ontamalimab) included in the pharmacodynamic analyses were not included in the pharmacokinetic analyses
[a]The 75 mg treatment group includes those who escalated from ontamalimab 75 mg to 225 mg and those who did not escalate.
[b]The 225 mg treatment group includes only patients who were assigned to receive ontamalimab from the beginning of OL1.
3M-FU, 3-month follow-up; PK, pharmacokinetic; SD, standard deviation

Geometric mean (90% CI) faecal calprotectin concentrations

Decreased consistently over 72 weeks from baseline (week 12 of TURANDOT) in OL1



	Baseline	4	8	12	16	20	24	32	72
75 mg[a]	142	141	129	133	122	107	92	93	59
225 mg[b]	155	141	138	133	129	112	110	102	63
All doses	297	282	267	266	251	219	202	195	122

Patients included those who previously received ontamalimab and those who received placebo in TURANDOT; this is therefore reflected in FC concentrations at baseline (week 12 of TURANDOT).

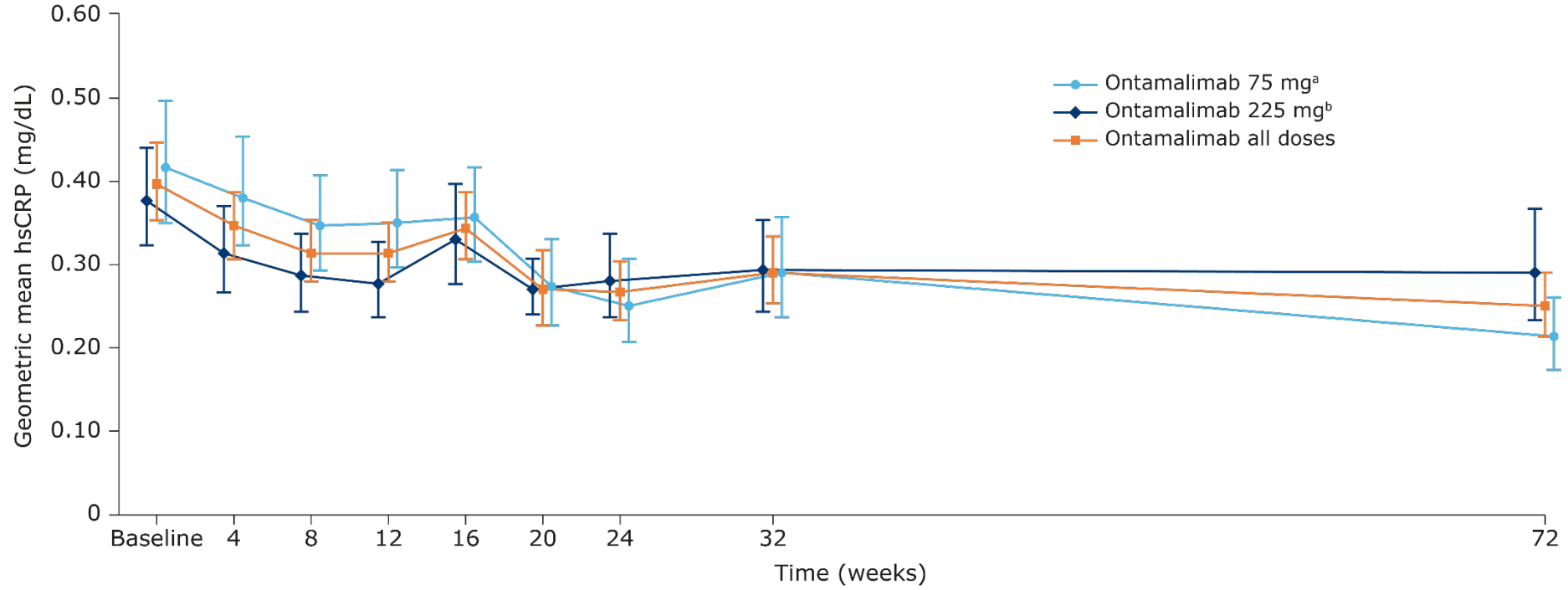
[a]The 75 mg treatment group includes those who escalated from ontamalimab 75 mg to 225 mg, and those who did not escalate.

[b]The 225 mg treatment group includes only patients who were assigned to receive ontamalimab from the beginning of OL1

CI, confidence interval; FC, faecal calprotectin; OL1, open label part 1

Geometric mean (90% CI) high sensitivity C-reactive protein concentrations

Decreased consistently over 72 weeks from baseline (week 12 of TURANDOT) in OL1



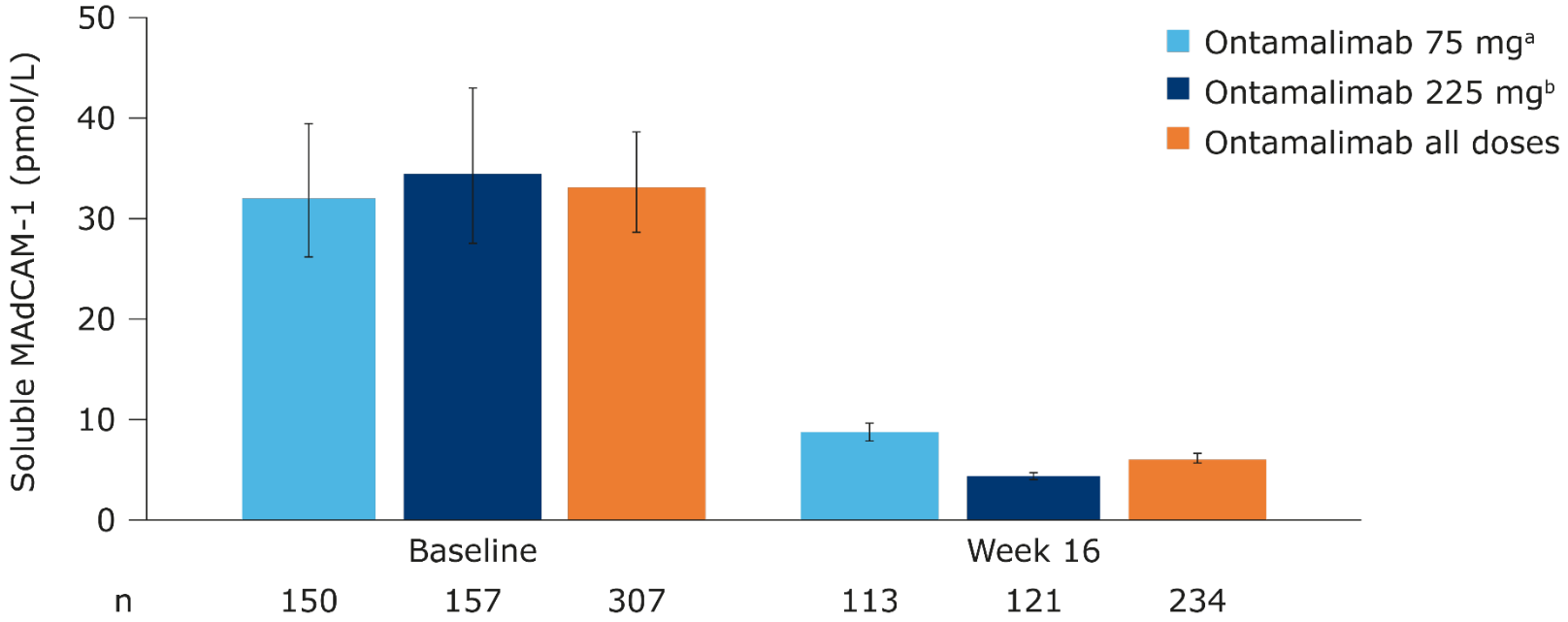
	Baseline	4	8	12	16	20	24	32	72
75 mg[a]	160	156	154	155	150	121	113	109	82
225 mg[b]	162	161	158	155	146	125	123	113	83
All doses	322	317	312	310	296	246	236	222	165

Patients included those who previously received ontamalimab and those who received placebo in TURANDOT; this is therefore reflected in hsCRP concentrations at baseline (week 12 of TURANDOT).
[a]The 75 mg treatment group includes those who escalated from ontamalimab 75 mg to 225 mg, and those who did not escalate.
[b]The 225 mg treatment group includes only patients who were assigned to receive ontamalimab from the beginning of OL1.
CI, confidence interval; hsCRP, high-sensitivity C-reactive protein; OL1, open label part 1

Geometric mean (90% CI) serum concentrations of free soluble MAdCAM-1

Lower at week 16 than baseline (week 12 of TURANDOT) for all patients

- Ontamalimab binds to MAdCAM-1, which is present on endothelial cells and in serum, predominantly in the intestinal tract and specialized intestinal lymphoid tissue[1]
- Soluble MAdCAM-1 levels were measured as a pathway-specific marker of ontamalimab action
- Geometric mean soluble MAdCAM-1 levels were ~250 pmol/L at baseline in the feeder study TURANDOT



Patients included those who previously received ontamalimab and those who received placebo in TURANDOT; this is therefore reflected in MAdCAM-1 concentrations at baseline (week 12 of TURANDOT).
[a]The 75 mg treatment group includes those who escalated from ontamalimab 75 mg to 225 mg and those who did not escalate.
[b]The 225 mg treatment group includes only patients who were assigned to receive ontamalimab from the beginning of OL1
CI, confidence interval; MAdCAM-1, mucosal addressin cell adhesion molecule-1

1. Feagan BG *et al. N Engl J Med* 2013;**369:**699–710.

Conclusions

- Ontamalimab treatment is associated with a reduction in free soluble MAdCAM-1, consistent with its mode of action, and with long-term reductions in FC and hsCRP
- Phase 3 clinical trials are currently underway, which should provide further evidence of the potential for ontamalimab to fulfil unmet therapeutic need in IBD

FC, faecal calprotectin; hsCRP, high-sensitivity C-reactive protein; MAdCAM-1, mucosal addressin cell adhesion molecule-1

Acknowledgements

- We thank investigators and participants at all sites involved in this study
- TURANDOT II was sponsored by Shire (a member of the Takeda group of companies) and Pfizer
- Medical writing support with the preparation of this presentation was provided by Emma Saxon of PharmaGenesis London, UK and funded by Shire (a member of the Takeda group of companies)