Sliznice křičí: „Zachraňte to střevo!“

JAK zasáhnout cíle STRIDE-II

doc. MUDr. Martin Bortlík, Ph.D.

Biologická léčba IBD a pokroky v chirurgické léčbě IBD
Hotel DUO, Praha, 21.-22.9.2023

STRIDE-I (2015) doporučovaly kompozitní léčebný cíl pro UC: klinický + endoskopický

Selecting therapeutic targets in IBD (STRIDE-I) programme

- Iniciován IOIBD
- Prozkoumat potenciál léčebných cílů u IBD pro sestavení T2T strategie klinického managementu
- Proces evidence-based expert consensus (systematické review literatury a opakovaných survey IOIBD členů)
- Skupina odsouhlasila a publikovala 12 doporučení jak pro CD tak i UC: STRIDE-I

T2T doporučení u CD

Composite endpoint

Clinical/PRO remission AND **Endoscopic remission**

Target: Resolution of abdominal pain and normalisation of bowel habit

- Resolution of symptoms alone is not a sufficient target
- Patients' individual goals should also be addressed

Target: Absence of ulceration

- Should be assessed within 6–9 months after start of therapy
- When endoscopy cannot adequately evaluate inflammation, assess resolution of inflammation by cross-sectional imaging

Adjunctive measures

Biomarkers: CRP and FCP are adjunctive measures of inflammation, not targets, for monitoring CD
Histology: Histologic remission is not considered a target

T2T doporučení u UC

Composite endpoint

Clinical/PRO remission AND **Endoscopic remission**

Target: Resolution of rectal bleeding and normalisation of bowel habit

- Resolution of symptoms alone is not a sufficient target
- Assessed at minimum of 3 months until resolution
- Assessed at least every 6–12 months after resolution

Target: Resolution of friability and ulceration at flexible sigmoidoscopy or colonoscopy

- Should be assessed at 3 months during active phase
- MES of 0 is optimal target, with subscore of 1 should be minimum target

Adjunctive measures*

Biomarkers: CRP and FCP are adjunctive measures of inflammation, not targets, for monitoring UC
Histology: Histologic remission is not considered a target due to lack of evidence of clinical utility

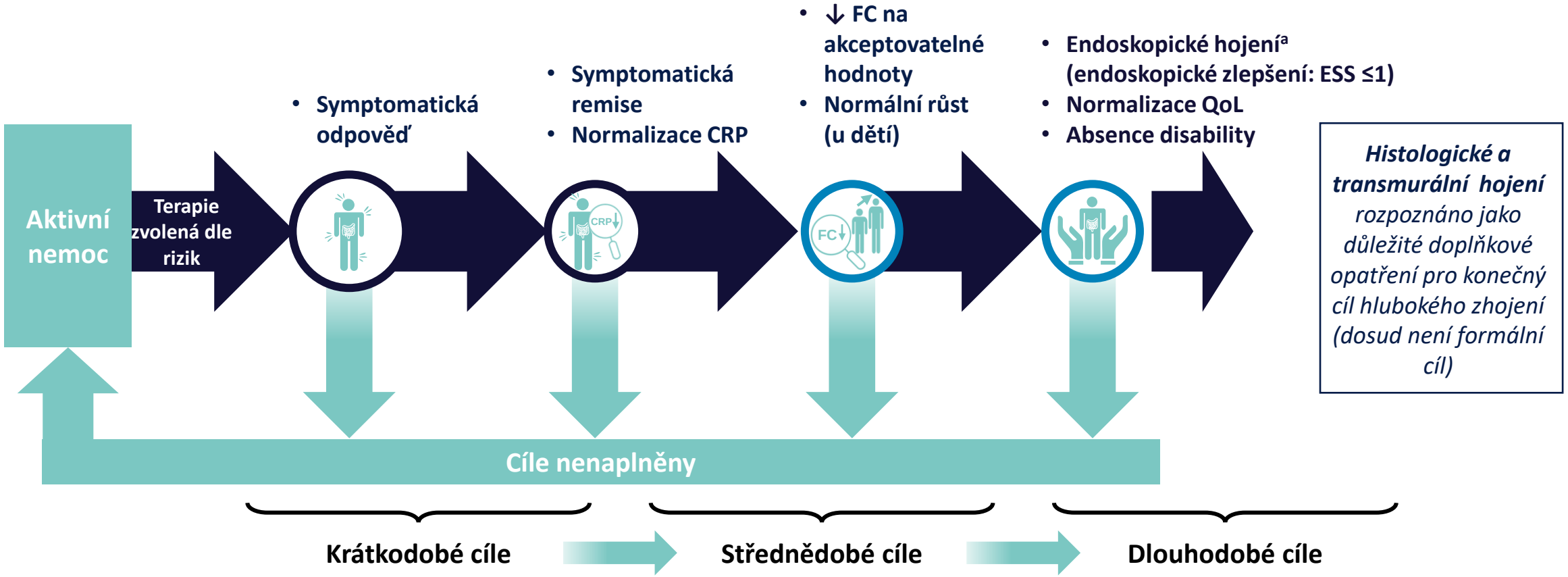
*Cross-sectional imaging is not a target in UC

CD, Crohn's disease; **CRP**, C-reactive protein; **FCP**, faecal calprotectin; **IBD**, inflammatory bowel disease; **IOIBD**, International Organization for the Study of IBD; **MES**, Mayo Endoscopic Subscore; **PRO**, patient-reported outcome; **T2T**, treat-to-target; **UC**, ulcerative colitis.

Peyrin-Biroulet L, *et al*. Am J Gastroenterol 2015;110:1324–38.

STRIDE-II: Treat-to-target přístup se však dále posunul

Ve spojení s klinickými cíli doporučuje STRIDE-II jako dlouhodobé cíle pro pacienty s UC nutnost endoskopického hojení, zlepšení QoL související se zdravím pacienta a snížení disability.



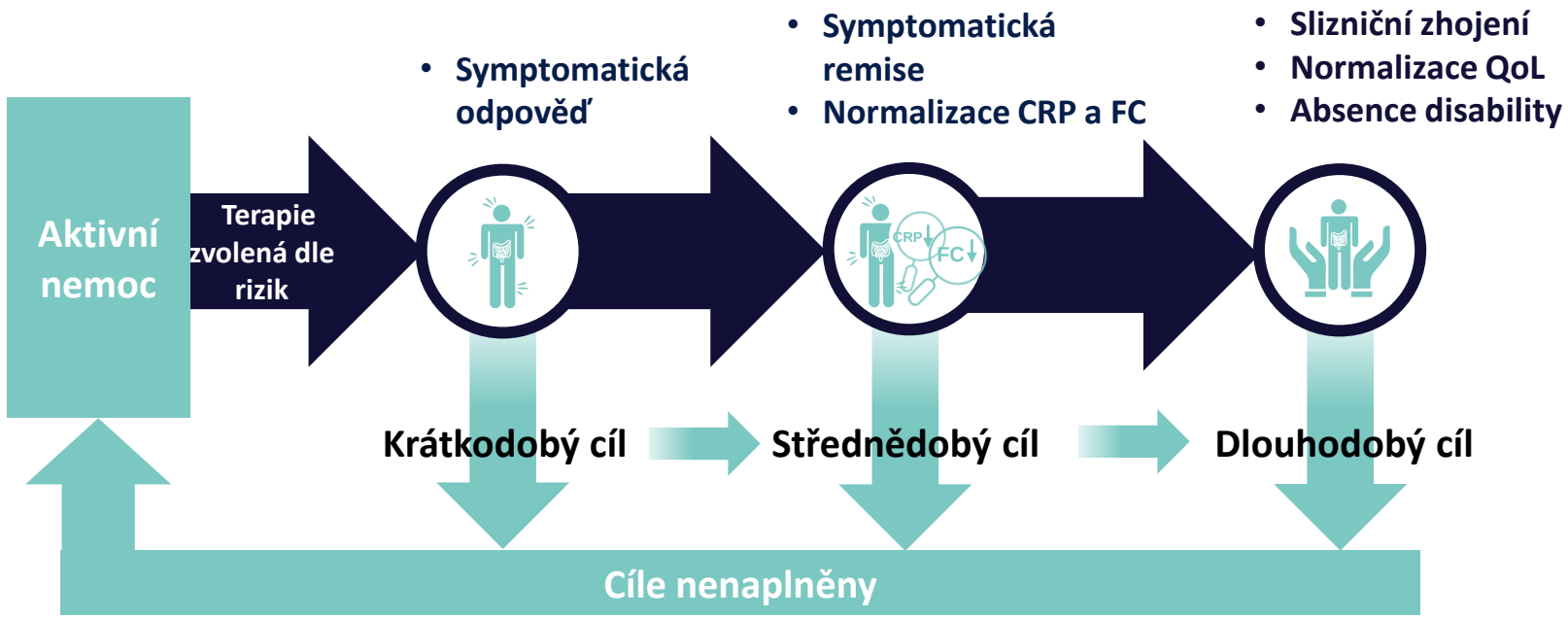
[a]Referred to as "mucosal healing" in some publications
CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis

Turner D, et al. Gastroenterology 2021;160:1570–83

Doporučení Pracovní skupiny pro IBD

Doporučení Pracovní skupiny pro idiopatické střevní záněty pro diagnostiku a medikamentózní léčbu ulcerózní kolitidy

M. Bortlík[1–4], D. Ďuricová[5], L. Hrdlička[6], P. Matějková[6], A. Novotný[7], P. Drastich[8], V. Mandys[9], P. Mináriková[2], B. Pipek[10], I. Mikoviny Kajzrlíková[11], L. Nedbalová[12], J. Koželuhová[13], N. Machková[5], V. Zbořil[14], L. Prokopová[14], P. Kohout[15], Z. Šerclová[16], M. Vašátko[8], T. Douda[17], J. Stehlík[18], K. Mareš[19], M. Lukáš[5]



Terapeutické cíle

Stanovisko 8

U pacientů s UC je krátkodobým terapeutickým cílem symptomatická odpověď, střednědobým cílem je klinická remise a normalizace biomarkerů a dlouhodobým cílem je zhojení sliznice, normalizace kvality života a eliminace invalidity. Uvedených cílů by mělo být dosaženo bez dlouhodobé léčby systémovými kortikoidy [EL4].

CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; UC, ulcerative colitis

Bortlík, et al. Gastroent Hepatol 2022;76(1): 13-28

Baseline demografické charakteristiky UC

Charakteristika onemocnění

Trvání onemocnění

Mean, years

7.3–8.6

Závažnost onemocnění

Full Mayo Score ≤9, %	Full Mayo Score >9, %
47.1–50.9	49.1–52.9

Rozsah onemocnění

Left-sided, %	Extensive pancolitis, %
48.1–49.5	50.5–51.6

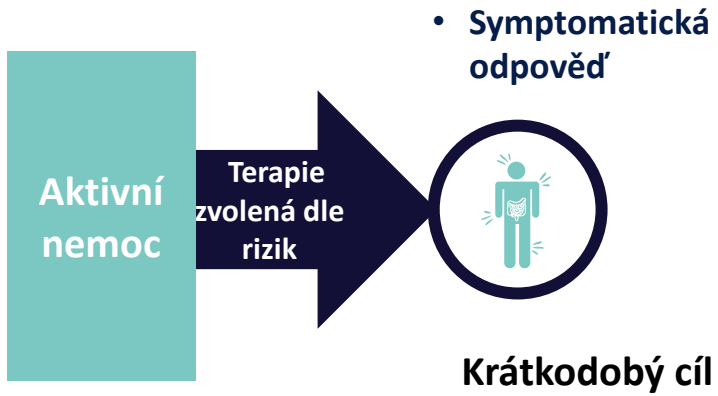
Baseline Bio-IR statut a předchozí medikace

Bio-IR, %	Number of prior biologics >1, %	Prior anti-TNF use, %	Prior vedolizumab use, %	Corticosteroid use, %
50.7–52.7	66.5–67.3	47.8–51.1	26.7–28.5	34.6–38.9

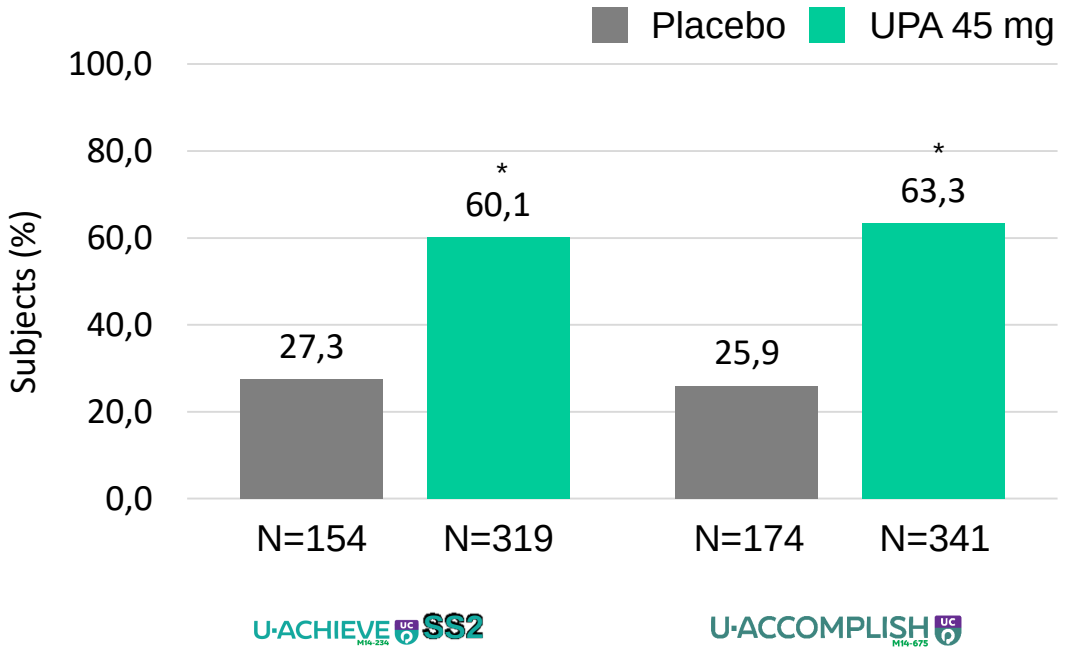
5ASA use, %	MTX use, %
67–69	0.6–2

1. Danese S, et al. OP24. European Crohn's and Colitis Organisation 2021 Congress.
2. Vermeire S, et al. OP23. European Crohn's and Colitis Organisation 2021 Congress.

Symptomatická odpověď



Symptomatická (klinická) odpověď v týdnu 2 dle částečného adaptovaného Mayo skóre



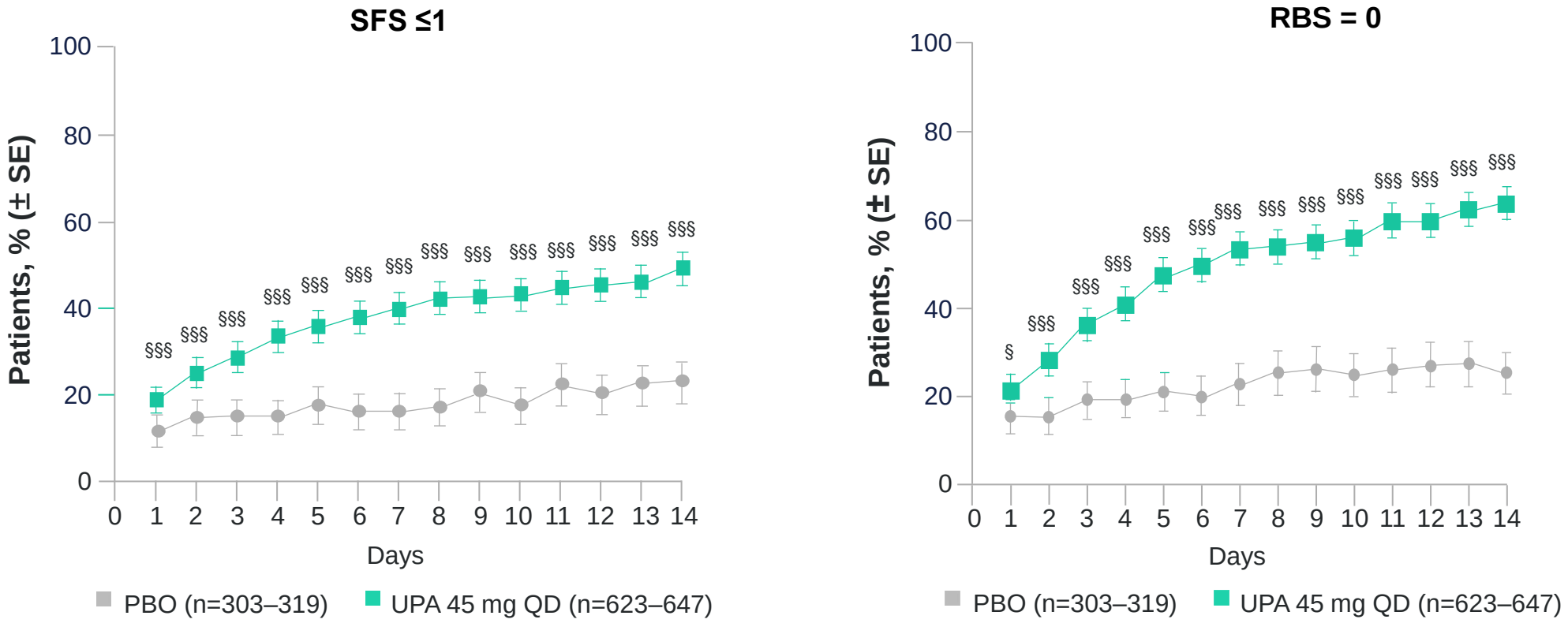
* p< 0.001 vs placebo

Wk 2 Clinical Response (Partial Adapted Mayo): Decrease in Partial Adapted Mayo score ≥ 1 point and ≥ 30% from Baseline, PLUS a decrease in RBS ≥ 1 or an absolute RBS ≤ 1

RBS, rectal bleeding subscore; UPA, upadacitinib; wk, week

Denní průběh dosažení SFS ≤1 a RBS = 0

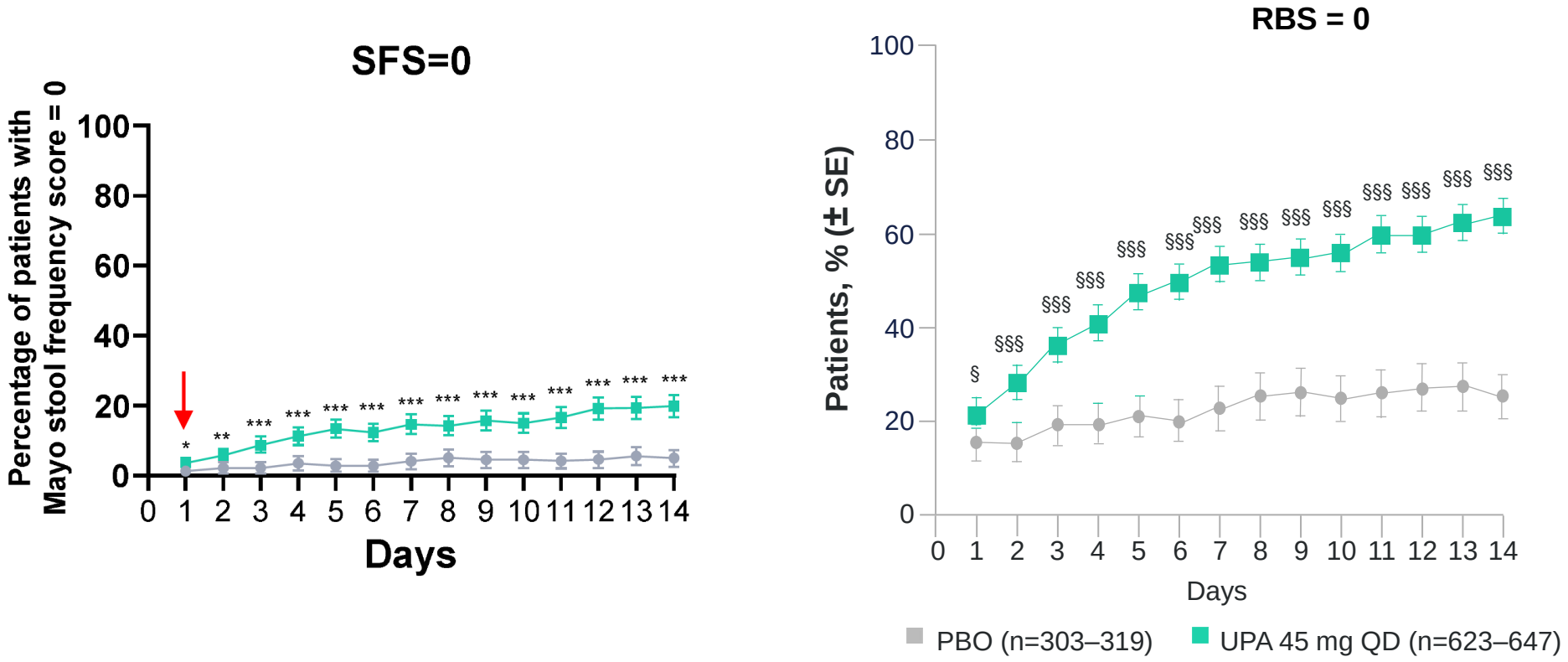
Post-hoc analýza: Poolovaná analýza U-ACHIEVE a U-ACCOMPLISH
Symptomatická úleva (SFS ≤1 a RBS = 0) od dne 1 do dne 14



Error bars are ± SE. §Nominal p≤0.05; §§§nominal p≤0.001 vs PBO. P-values are nominal and not multiplicity controlled.[2] Limitations: Post-hoc analyses lack multiplicity control. No statistical or clinical conclusions can be drawn.
PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; SE, standard error; SFS, stool frequency subscore; UPA, upadacitinib.
1. Vermeire S, et al. Presented at United European Gastroenterology Week, 3–5 October 2022, virtual: DOP38; 2. Danese S, et al. *Lancet*. 2022;399:2113–28 (supplementary data).

Denní průběh dosažení SFS = 0 a RBS = 0

Post-hoc analýza: Poolovaná analýza U-ACHIEVE a U-ACCOMPLISH
Symptomatická úleva (SFS = 0 a RBS = 0) od dne 1 do dne 14



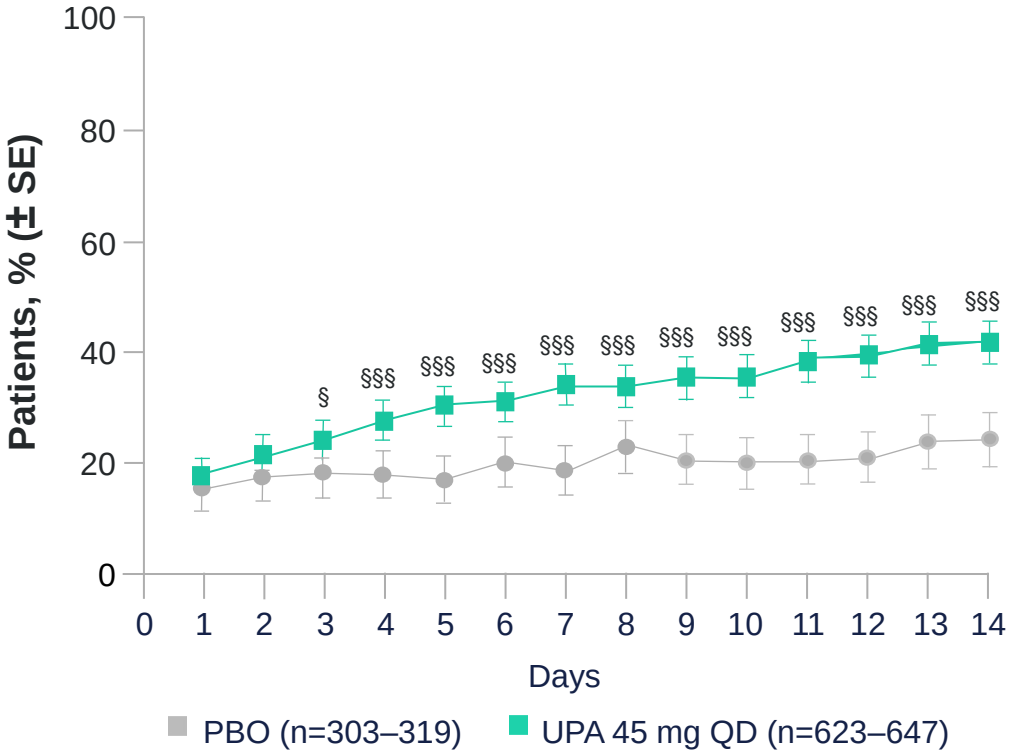
Error bars are ± SE. §Nominal p≤0.05; §§§nominal p≤0.001 vs PBO. P-values are nominal and not multiplicity controlled.[2] Limitations: Post-hoc analyses lack multiplicity control. No statistical or clinical conclusions can be drawn.
PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; SE, standard error; SFS, stool frequency subscore; UPA, upadacitinib.
1. Vermeire S, et al. Presented at United European Gastroenterology Week, 3–5 October 2022, virtual: DOP38; 2. Danese S, et al. *Lancet*. 2022;399:2113–28 (supplementary data).

Abdominální bolest = 0 a absence nutkání na stolici

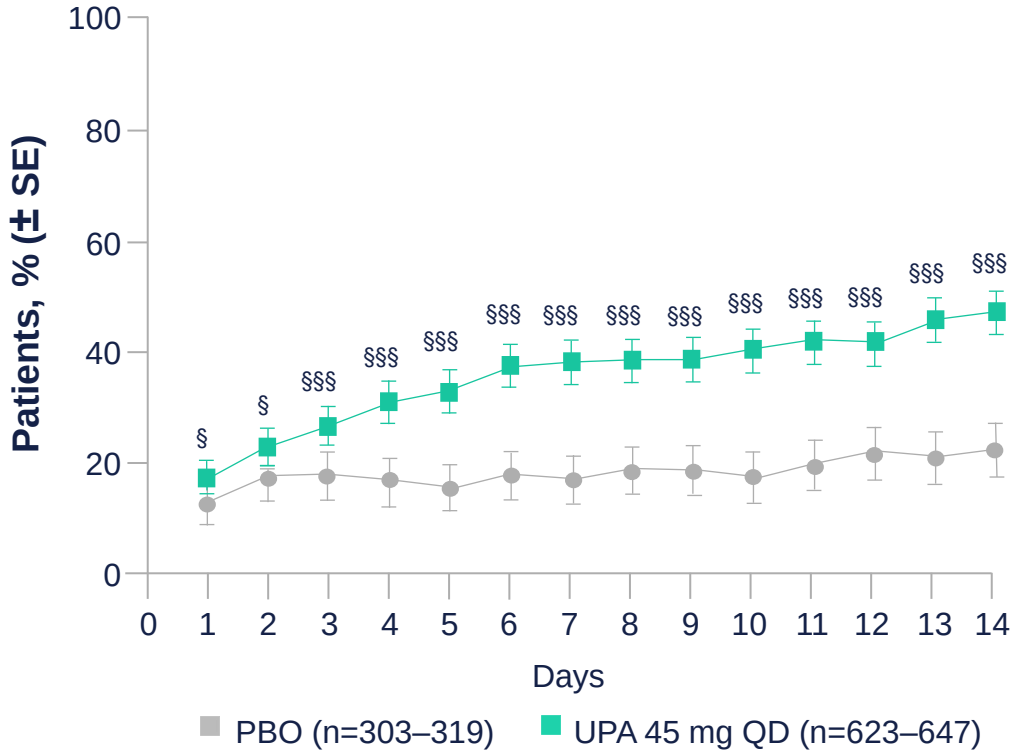
Post-hoc analýza: Poolovaná analýza U-ACHIEVE a U-ACCOMPLISH

Symptomatická úleva (abdominální bolest = 0 a absence nutkání na stolici) ode dne 1 do dne 14

Skóre abdominální bolesti = 0



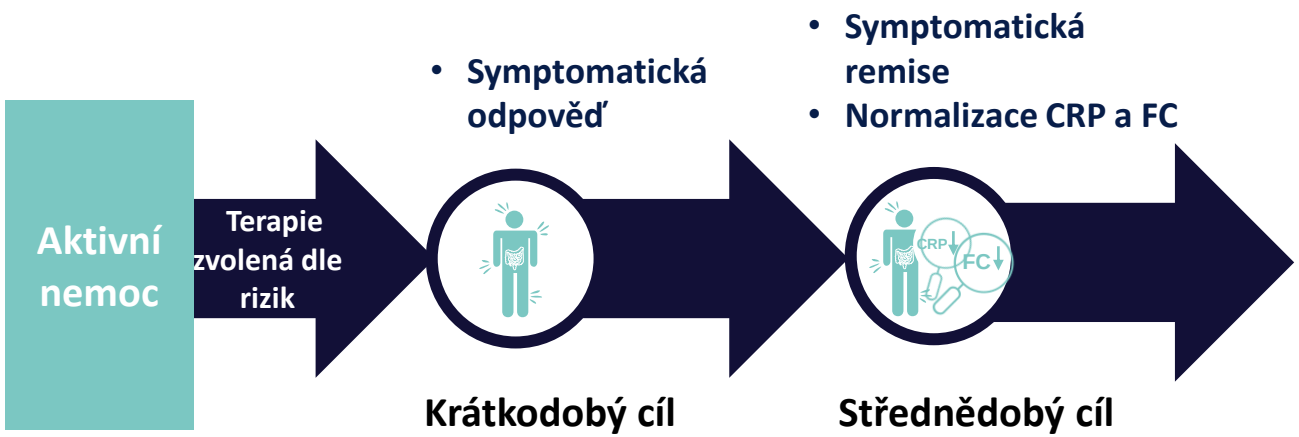
Absence nutkání na stolici



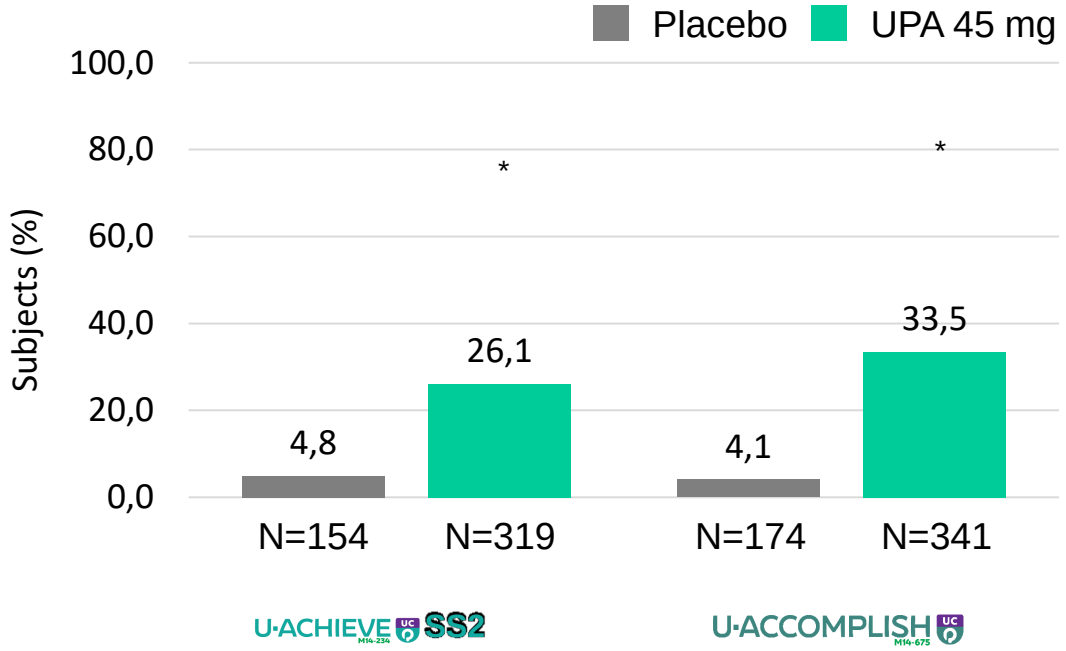
Error bars are ± SE. §Nominal p≤0.05; §§§nominal p≤0.001 vs PBO. P-values are nominal and not multiplicity controlled.[2] Limitations: Post-hoc analyses lack multiplicity control. No statistical or clinical conclusions can be drawn.
PBO, placebo; QD, once daily; SE, standard error; UPA, upadacitinib.

1. Vermeire S, et al. Presented at United European Gastroenterology Week, 3–5 October 2022, virtual: DOP38; 2. Danese S, et al. *Lancet*. 2022;399:2113–28 (supplementary data).

Symptomatická remise a normalizace CRP a FC



Klinická remise dle adaptovaného Mayo skóre v týdnu 8



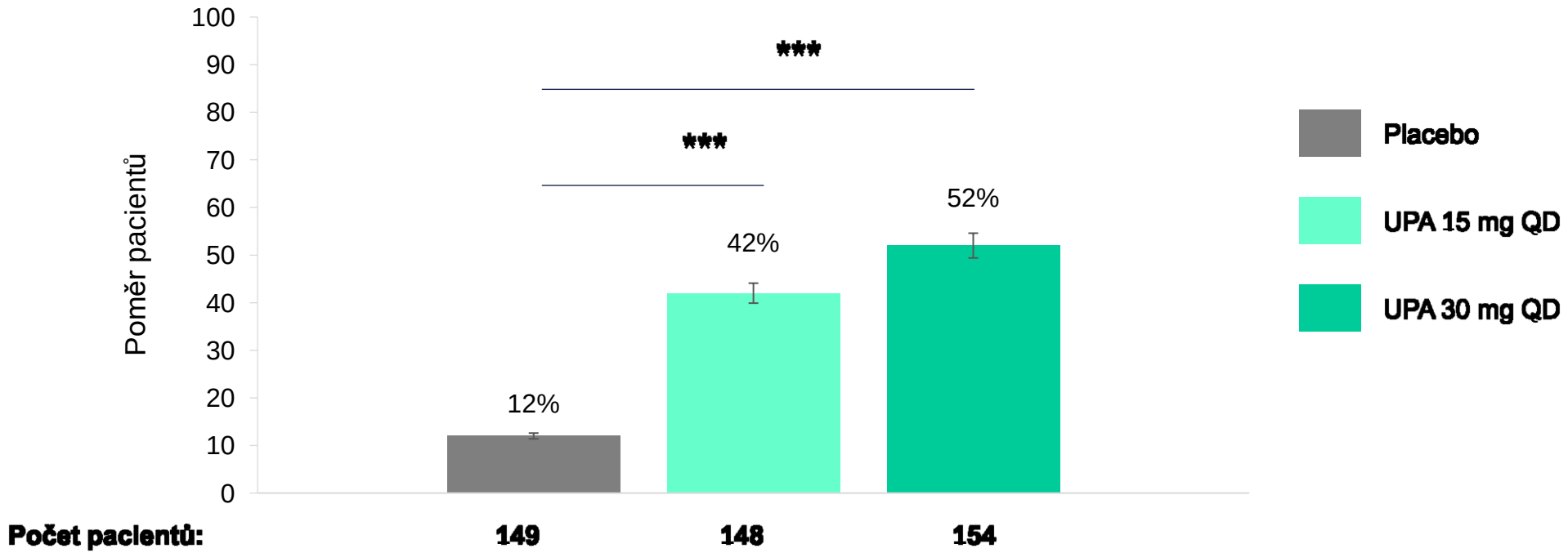
*P <0.001 vs placebo.
Clinical Remission: adapted Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS of 0, and endoscopic subscore ≤1.
ES, endoscopic subscore; QD, once daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore; UPA, upadacitinib.
CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; UC, ulcerative colitis

Danese S, et al. OP24. European Crohn's and Colitis Organisation 2021 Congress.; Vermeire S, et al. OP23. European Crohn's and Colitis Organisation 2021 Congress.
Upraveno dle Bortlík, et al. Gastroent Hepatol 2022;76(1): 13-28

Symptomatická remise a normalizace CRP a FC

Symptomatická (klinická) remise v týdnu 52 dle adaptovaného Mayo skóre

52



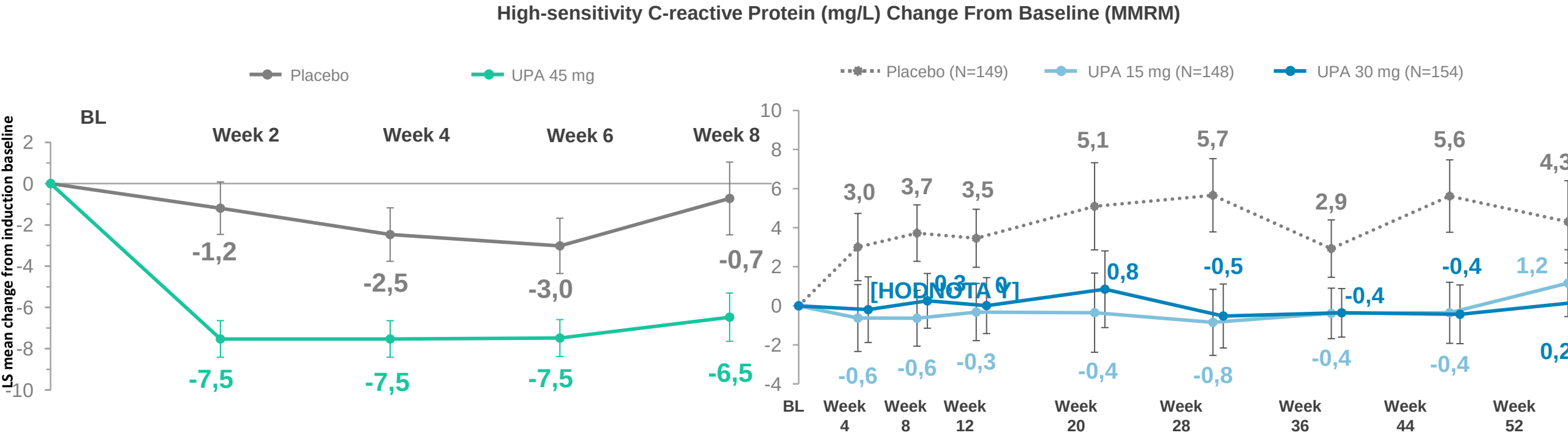
Clinical Remission: adapted Mayo score ≤2, with SFS ≤1 and not greater than baseline, RBS of 0, and endoscopic subscore ≤1.
ES, endoscopic subscore; QD, once daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore; UPA, upadacitinib.
Results are based on non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19. Statistical significance is determined via the graphical multiple testing procedure controlling the overall type I error rate of all primary and key secondary endpoints at the 0.05 level. Error bars are ±95% CI. ***P-value <0.001. QD, once daily.

Panaccoine R, et al. United European Gastroenterology Week 2021 Congress.

Symptomatická remise a normalizace CRP a FC

Změny hladiny CRP v indukční fázi 8

Změna hladin CRP v udržovací fázi 52



BL, baseline; Fcal, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; LS, least squares; MMRM, mixed-effect model repeat measurement; UPA, upadacitinib.

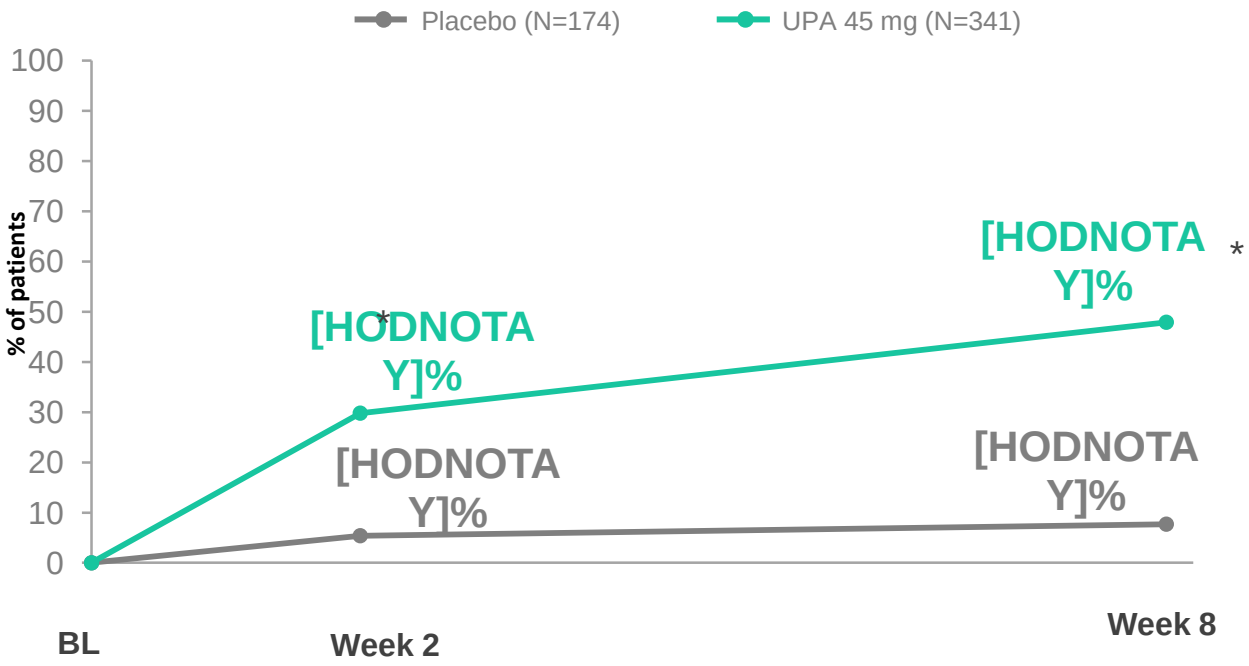
1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128.

Symptomatická remise a normalizace CRP a FC

Hladiny fekálního kalprotektinu v indukci

8

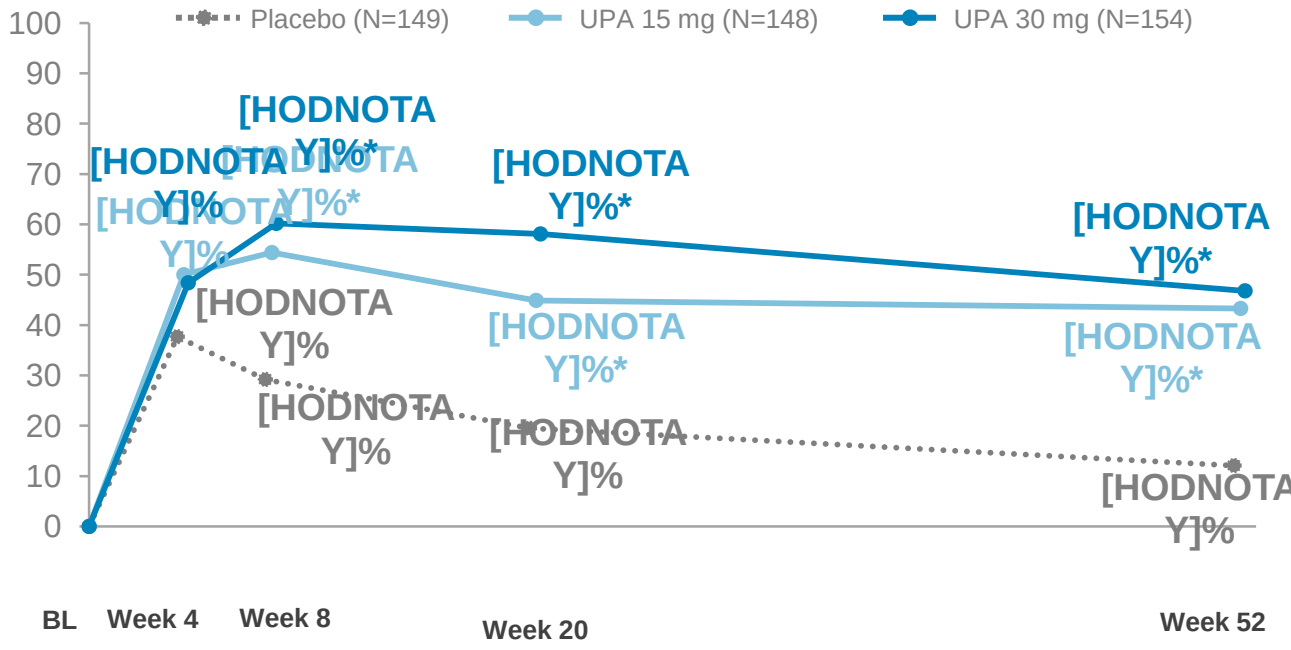
Proportion of Patients Achieving Fecal Calprotectin <150 mg/kg up to 8 Weeks



Hladiny fekálního kalprotektinu v udržovací fázi

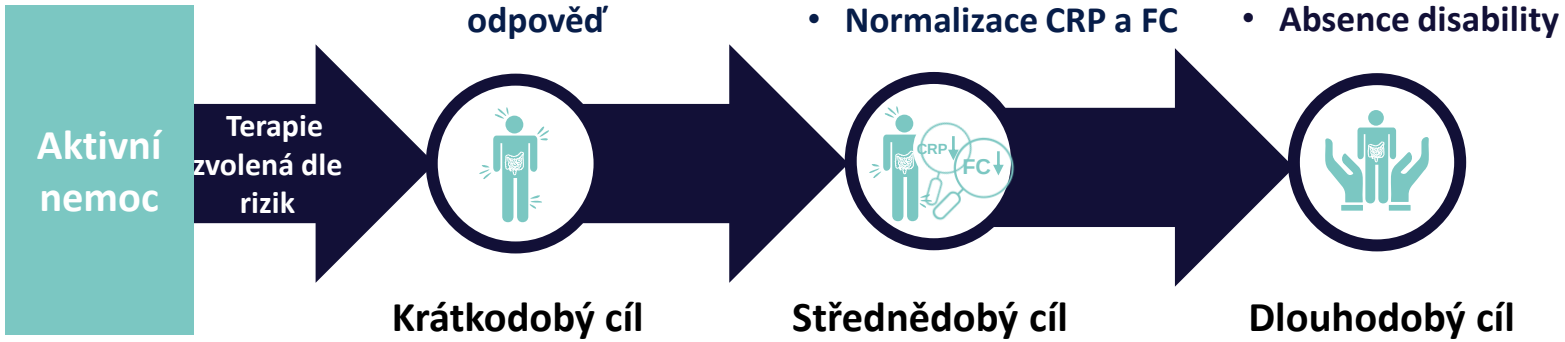
52

Proportion of Patients Achieving Fecal Calprotectin <150 mg/kg up to 52 Weeks

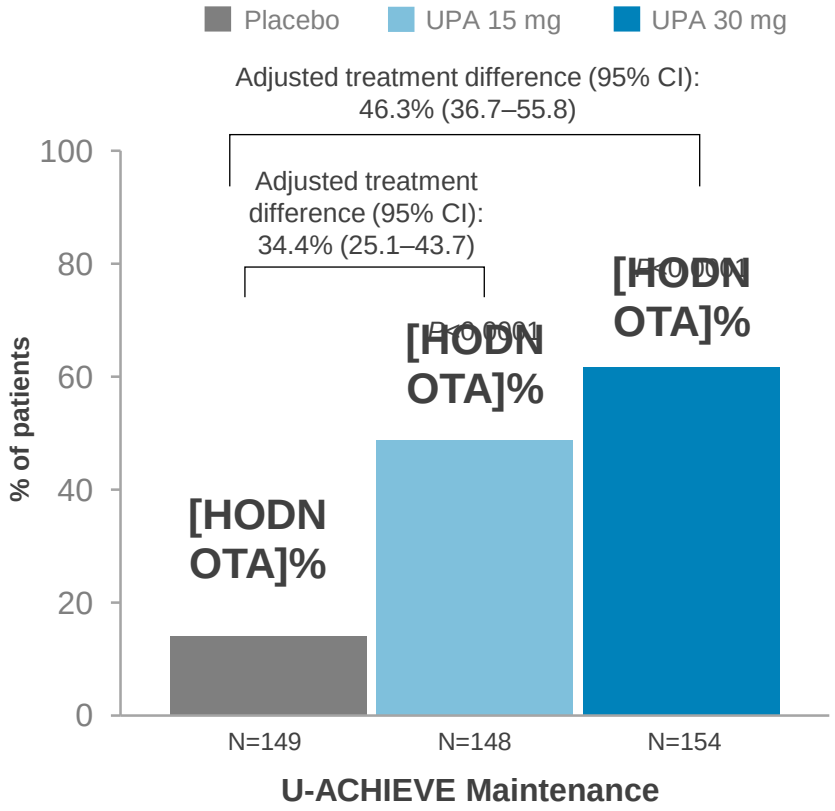


*P values of P<0.001 are nominal and cannot be considered for statistical significance.
BL, baseline; Fcal, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; UPA, upadacitinib.
1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128.

Slizniční (z)hojení, normalizace kvality života a absence disability



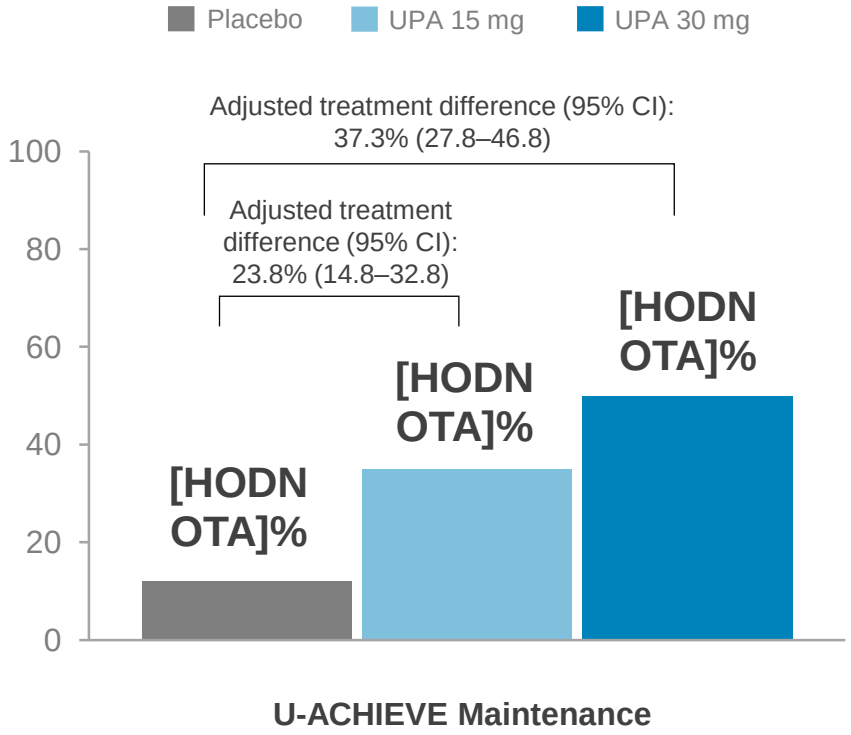
Endoskopické zlepšení (ESS≤1) v týdnu 52



CI, confidence interval; UPA, upadacitinib.
1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128. Upraveno dle Bortlík, et al. Gastroent Hepatol 2022;76(1): 13-28
CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; UC, ulcerative colitis

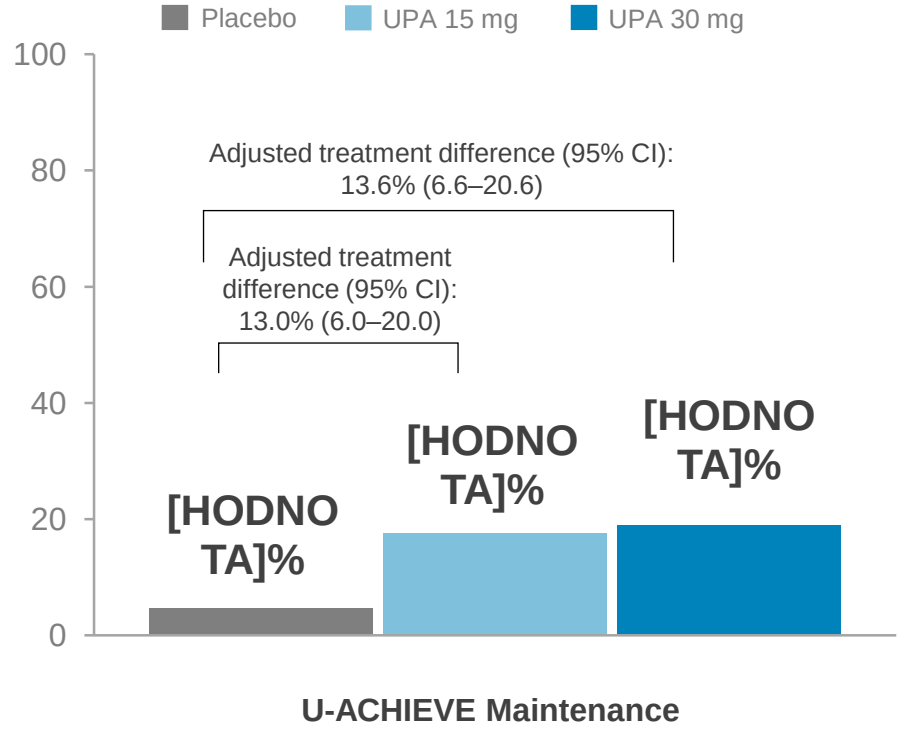
Slizniční (z)hojení, normalizace kvality života a absence disability

HEMI v týdnu 52



Geboes ≤3.1: neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue[2]

Slizniční zhojení v týdnu 52



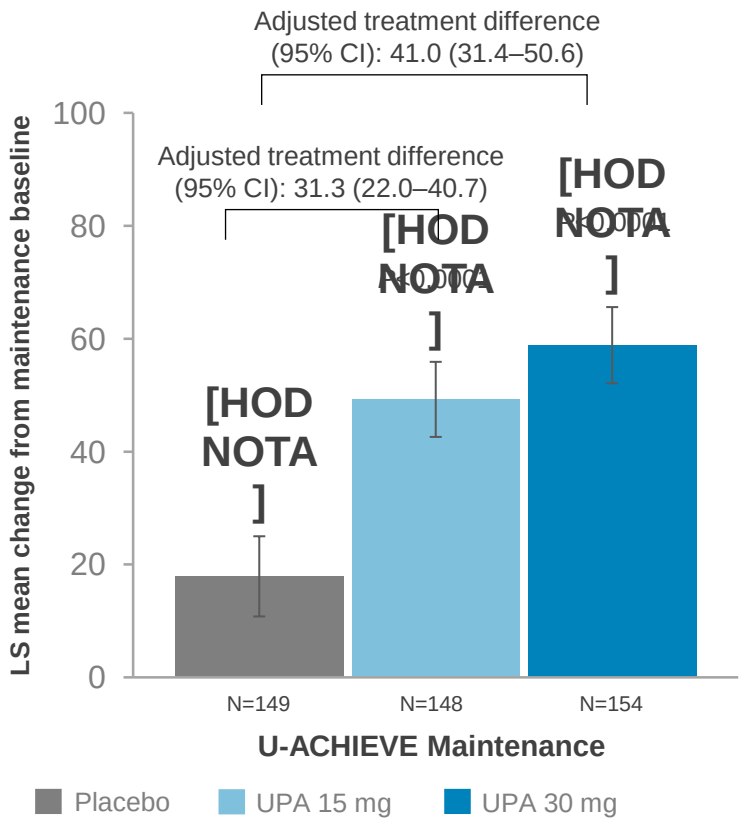
Geboes <2: no neutrophil or eosinophil infiltration in crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue[2]

CI, confidence interval; HEMI, histologic-endoscopic mucosal improvement; UPA, upadacitinib.

1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128. 2. Geboes K et al. *Gut*. 2000;47(3):404-409.

Slizniční (z)hojení, normalizace kvality života a absence disability

Změna od baseline v IBDQ v týdnu 52



*Data were analyzed by non-responder imputation incorporating multiple imputation to handle missing data due to COVID-19.
CI, confidence interval; IBDQ, Inflammatory Bowel Disease Questionnaire; LS, least squares; UPA, upadacitinib.
1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128.

Treat-to-target koncept v klinické praxi

Methods: Intention to treat-to-target score

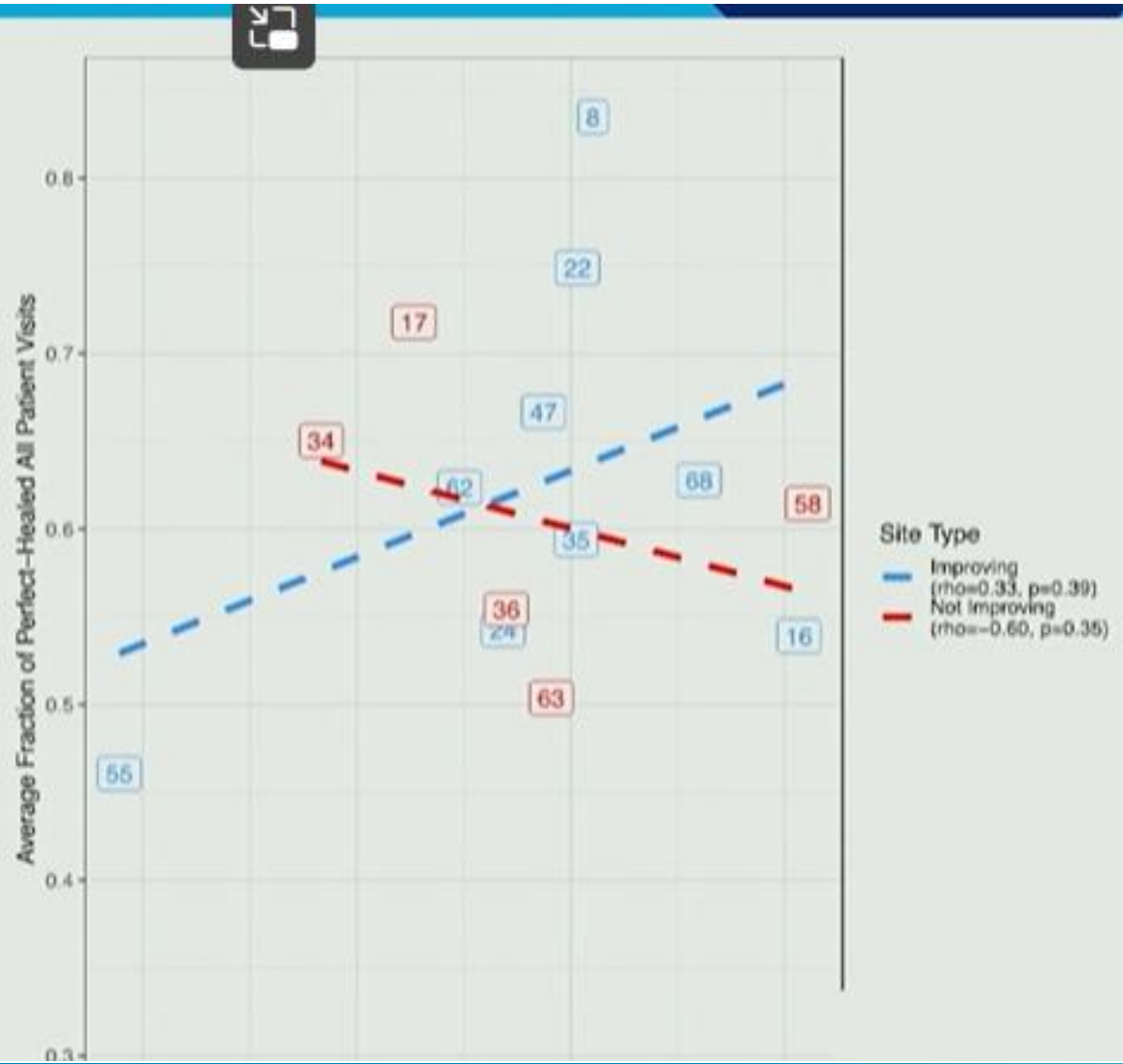
- Among patients who had not achieved target of mucosal healing
  1. Was treat-to-target discussed? – YES/NO
  2. Was endoscopy/imaging or calprotectin performed within the preceding 12m? - YES/NO
  3. Is treatment being changed, or was recently changed, or be determined by TDM? - YES/NO

If **YES to all three questions**, then **TTT score = 1**, otherwise = 0 (categorical)

Minimum threshold for clinically meaningful signal of improvement defined ***a priori*** as ≥2% increase per month

Treat-to-target koncept v klinické praxi

Proportion of all visits in which patients were in mucosal healing, increasing in sites with improvement in TTT score



Singh S, et al. DDW 2023, Chicago, IL

Treat-to-target koncept v klinické praxi

Proportion of all visits in which patients were in steroid free clinical remission, increasing in sites with improvement in TTT score

Singh S, et al. DDW 2023, Chicago, IL

Bezpečnost v průběhu indukčních studií

TEAE, n (%)	U·ACHIEVE M14-234 SS2		U·ACCOMPLISH M14-675	
	Placebo (N = 155)	UPA 45 mg QD (N = 319)	Placebo (N = 177)	UPA 45 mg QD (N = 344)
Závažné AE	9 (5,8)	8 (2,5)	8 (4,5)	11 (3,2)
Závažné infekce	2 (1,3)	5 (1,6)	1 (0,6)	2 (0,6)
Malignity	0	0	0	0
Gastrointestinální perforace	0	0	1 (0,6)	0
Posuzované MACE	0	0	0	0
Posuzované VTEs	0	0	1 (0,6)	0
Úmrtí	0	0	0	0

Nejčastěji pozorovaným AE ve skupinách s UPA byly akné, zvýšení kreatinfosfokinázy (CPK)[a], nazofaryngitidy v M14-234 Substudie 2 a anémie v M14-675

[a]Increases in blood CPK were non-serious and did not lead to study drug discontinuation; patients with blood CPK increase were usually asymptomatic and no cases of rhabdomyolysis were reported.
MACE, major adverse cardiovascular event; QD, once daily; VTE, venous thrombotic event.

Vermeire S, et al. United European Gastroenterology Week 2021 Congress.

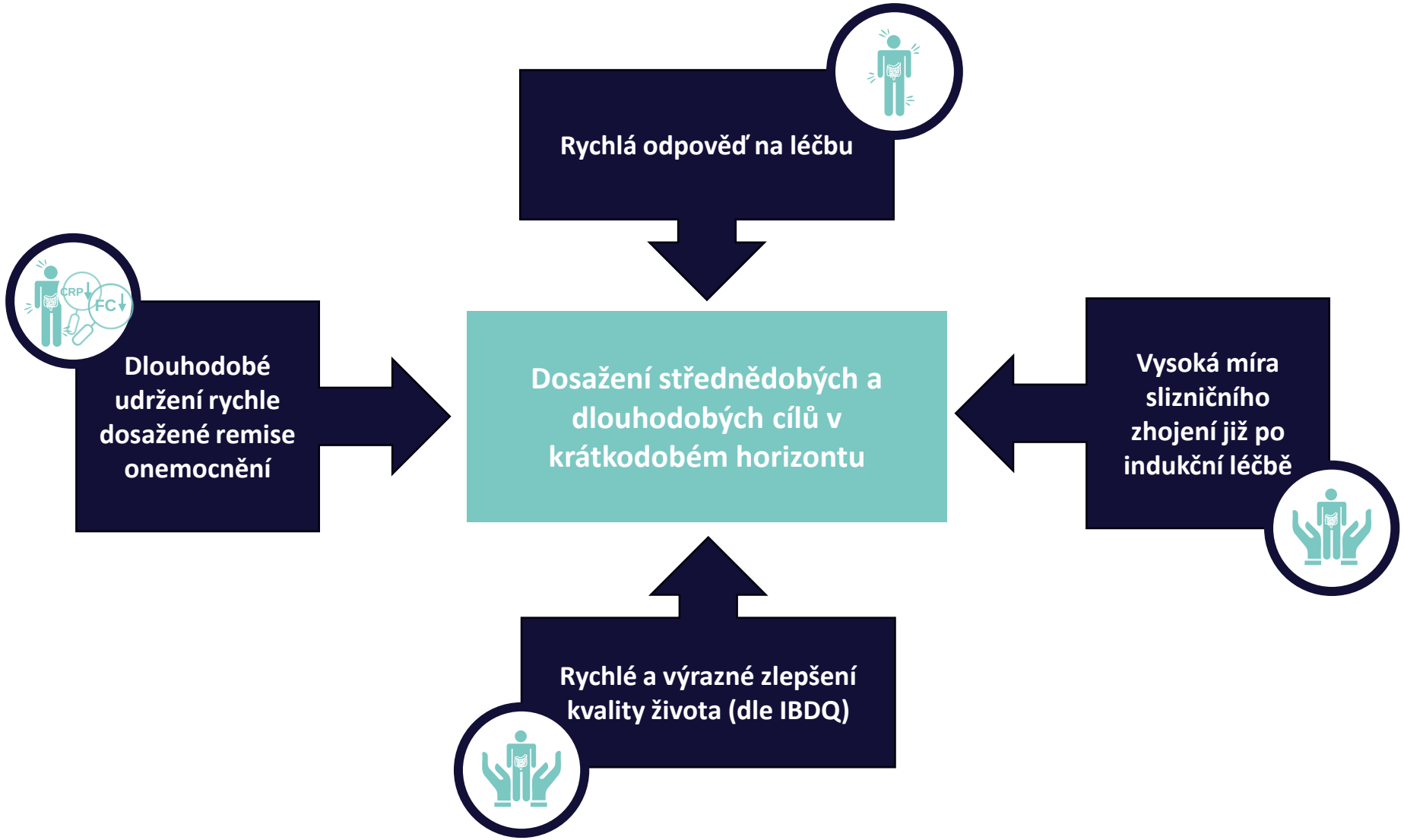
Bezpečnost v průběhu udržovací fáze až do 52 týdnů

TEAEs	Placebo	UPA 15 mg QD	UPA 30 mg QD
Nežádoucí účinek (AE), příhody/100 Pys	26,1	16,0	13,8
Závažné AE (SAE), příhody/100 Pys	21,9	12,6	10,6
Závažné infekce, příhody/100 PYs	6,2	4,9	3,0
AEs vedoucí k vysazení, příhody/100 Pys	24,3	7,6	7,9
Malignity mimo NMSC, # příhod	1	1	2
Gastrointestinální perforace, # příhod	1	0	0
Posuzované MACE, # příhod	1	0	1
Posuzované VTEs, # příhod[a]	0[b]	2	2
Úmrtí, # příhod	0	0	0

Nejčastěji pozorovanými AE ve skupinách s UPA v průběhu **52týdenní studie byly nazofaryngitidy, exacerbace UC a zvýšení** kreatinfosfokinázy (CPK)

[a]VTEs included: two events of PE in the UPA 15 mg group and two events of DVT in the UPA 30 mg group.
[b]One ovarian vein thrombosis was reported in the placebo group; however, this is not included as VTE, which is defined as DVT or PE.
N = 746 patients evaluated for safety.
DVT, deep vein thrombosis; MACE, major adverse cardiovascular event; PE, pulmonary embolism; PY, patient years;
QD, once daily; TEAE, treatment-emergent adverse event; UC, ulcerative colitis; UPA, upadacitinib; VTE; venous thrombotic event.

Treat-to-target přístup s upadacitinibem? Závěr...



CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis

Danese S et al. Lancet. 2022;399(10341):2113-2128.
Panaccione R et al. United European Gastroenterol J. 2021;9(10):1197-1221 LB11.
SmPC Rinvoq

Souhrn

1. Léčebné cíle se vyvíjejí: objektivní hodnocení zánětlivé aktivity
2. Léčba k cíli je v praxi realizovatelná a má efekt
3. Endoskopická remise (ESS = 0) je důležitým dlouhodobým cílem v UC, slizniční zhojení je proto v léčbě UC důležitou strategií
4. PROs a endoskopické endpointy nejsou konzistentně definovány mezi klinickými studiemi
5. V budoucnu budou zřejmě preferovány neinvazivní markery a další formy PROs
6. Klinické studie budoucnosti budou zaměřeny na „chorobu modifikující“ efekt

PRO, patient-reported outcome