

Terapie upadacitinibem ve světle STRIDE-II a SPIRIT

Martin Bortlík

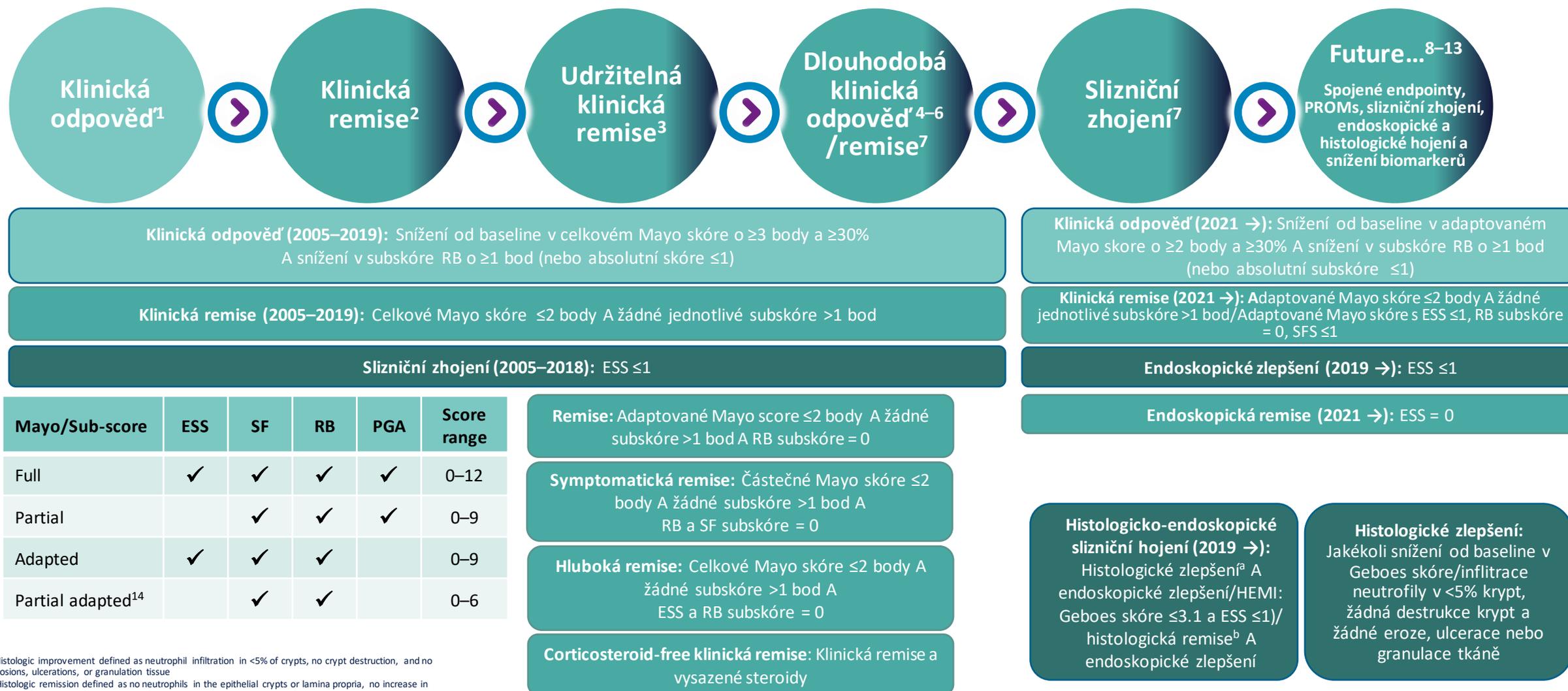
IBD FUTURE: setkání expertů, NH Prague, 19.5.2023

Hodnocení efektu léčby

- Odpověď vs. remise
- Čas hodnocení
- Způsob hodnocení
 - klinický stav (aktivita → tíže), PRO
 - laboratorní parametry (CRP, FC → feritin, albumin)
 - endoskopie
 - histologie
 - (zobrazovací metody)
- Místo hodnocení: ambulance vs. telemedicína
- Symptomy IBD vs. komplikace léčby vs. jiná příčina

Jaký je konkrétní cíl léčby?

Léčebné cíle v klinických studiích UC se stále vyvíjejí



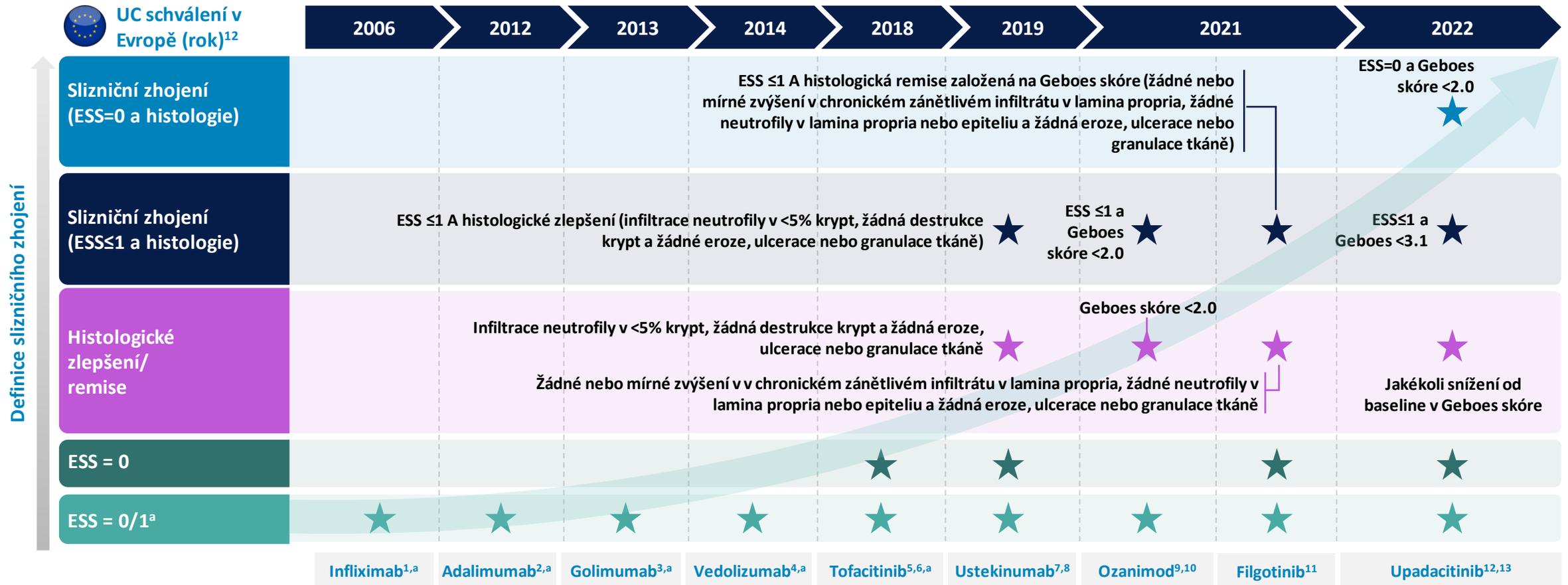
^aHistologic improvement defined as neutrophil infiltration in $< 5\%$ of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue

^bHistologic remission defined as no neutrophils in the epithelial crypts or lamina propria, no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue

ESS, endoscopic subscore; HEMI, histologic endoscopic mucosal improvement; PGA, physician's global assessment; PROM, patient-reported outcome measure; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis

1. Rutgeerts P, et al. N Engl J Med 2005;53:2462–76; 2. Reinisch W, et al. Gut 2011;60:780–7; 3. Sandborn WJ, et al. Gastroenterology 2012;142:257–65; 4. Sandborn WJ, et al. Gastroenterology 2014;146:85–95; 5. Sandborn WJ, et al. Gastroenterology 2014;146:96–109; 6. Feagan BG, et al. N Engl J Med 2013;369:699–710; 7. Sandborn WJ, et al. N Engl J Med 2017;376:1723–36; 8. Allen PB, et al. Expert Opin Biol Ther 2020;20:151–61; 9. Sands BE, et al. N Engl J Med 2019;381:1201–14; 10. Sandborn WJ, et al. Presented at: UEGW Virtual 2020: Oral Presentation LB02; 11. Sandborn WJ, et al. Gastroenterology 2020;158:2139–49; 12. Feagan BG, et al. Lancet 2021;397:2372–84; 13. Vermeire S, et al. J Crohns Colitis 2021;15(Suppl 1):S021–22; 14. Lewis JD, et al. Inflamm Bowel Dis 2008;14:1660–6

Slizniční endpointy v klinických studiích v UC se vyvíjejí tak, aby lépe odrážely význam slizničního zhojení



1. Rutgeerts P, et al. N Engl J Med 2005;353(23):2462–76; 2. Sandborn WJ, et al. Gastroenterology 2012;142:257–65; 3. Sandborn WJ, et al. Gastroenterology 2014;146:85–95; 4. Feagan BG, et al. N Engl J Med 2013;369:699–710; 5. Sandborn WJ, et al. N Engl J Med 2017;376:1723–36 supplementary appendix; 6. Tofacitinib smpc. Available at: <https://www.medicines.org.uk/emc/product/2500/smpc>. Accessed June 25, 2021; 7. Sands BE, et al. N Engl J Med 2019;381:1201–14; 8. Ustekinumab smpc. Available at: <https://www.medicines.org.uk/emc/product/4413/smpc>. Accessed June 25, 2021; 9. Sandborn W, et al. Am J Gastroenterol 2020;115(Suppl):S6–S7; 10. Sandborn WJ, et al. Presented at: UEGW Virtual 2020: Oral Presentation LB02; 11. Feagan BG, et al. Lancet 2021 397:2372–84; 12. Sandborn WJ, et al. Gastroenterology 2020;158:2139–49; 13. Sandborn WJ, et al. J Crohns Colitis 2019;13(Suppl 1):S009, abstract OP14.

^aESS ≤1 was referred to as “mucosal healing”; ESS, endoscopic subscore; FDA, Food and Drug Administration; UC, ulcerative colitis

STRIDE-I (2015) doporučovaly kompozitní léčebný cíl pro CD a 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

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

AND

Endoscopic remission

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

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

AND

Endoscopic remission

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

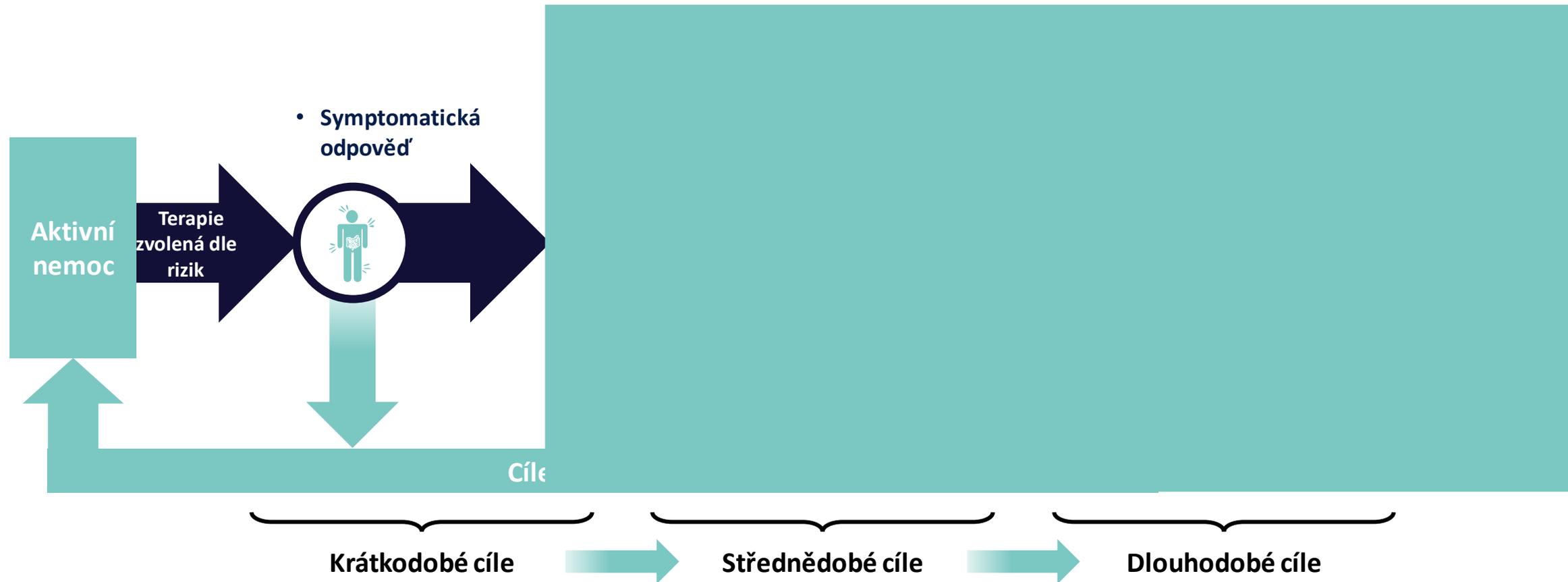
Histology: Histologic remission is not considered a target due to lack of evidence of clinical utility

*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.

Treat-to-target přístup se však dále posouvá



^aReferred to as "mucosal healing" in some publications

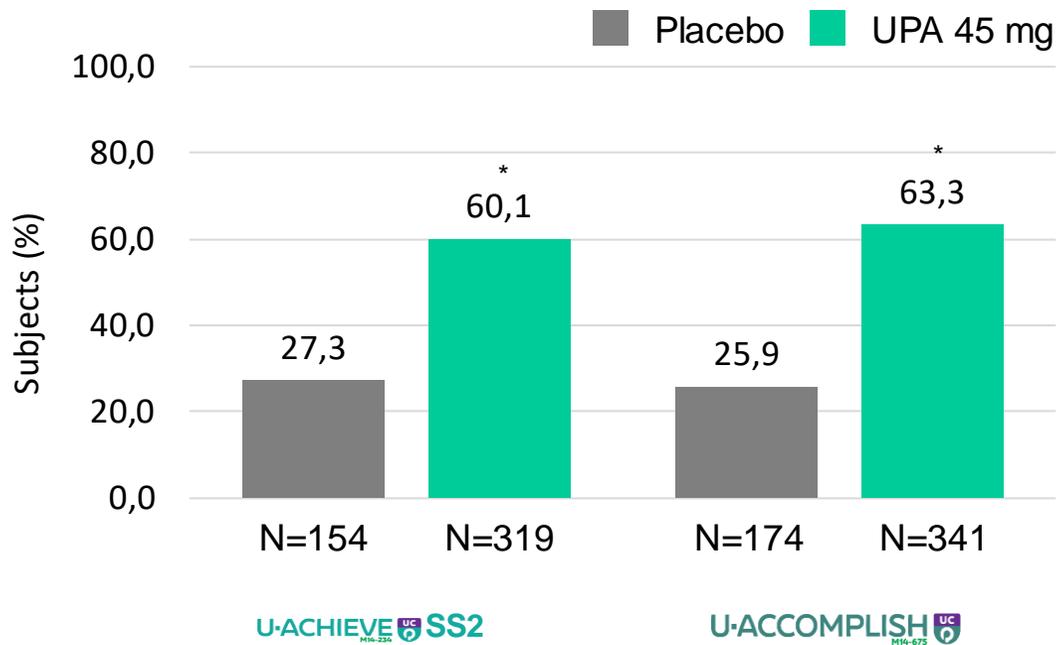
CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis

Requested copyright permission for Figure 2 in Turner D, et al. *Gastroenterology* 2021. Turner D, et al. *Gastroenterology* 2021;160:1570–83

Symptomatic response

Ulcerative colitis

Week 2 clinical response (Partial Adapted Mayo) score



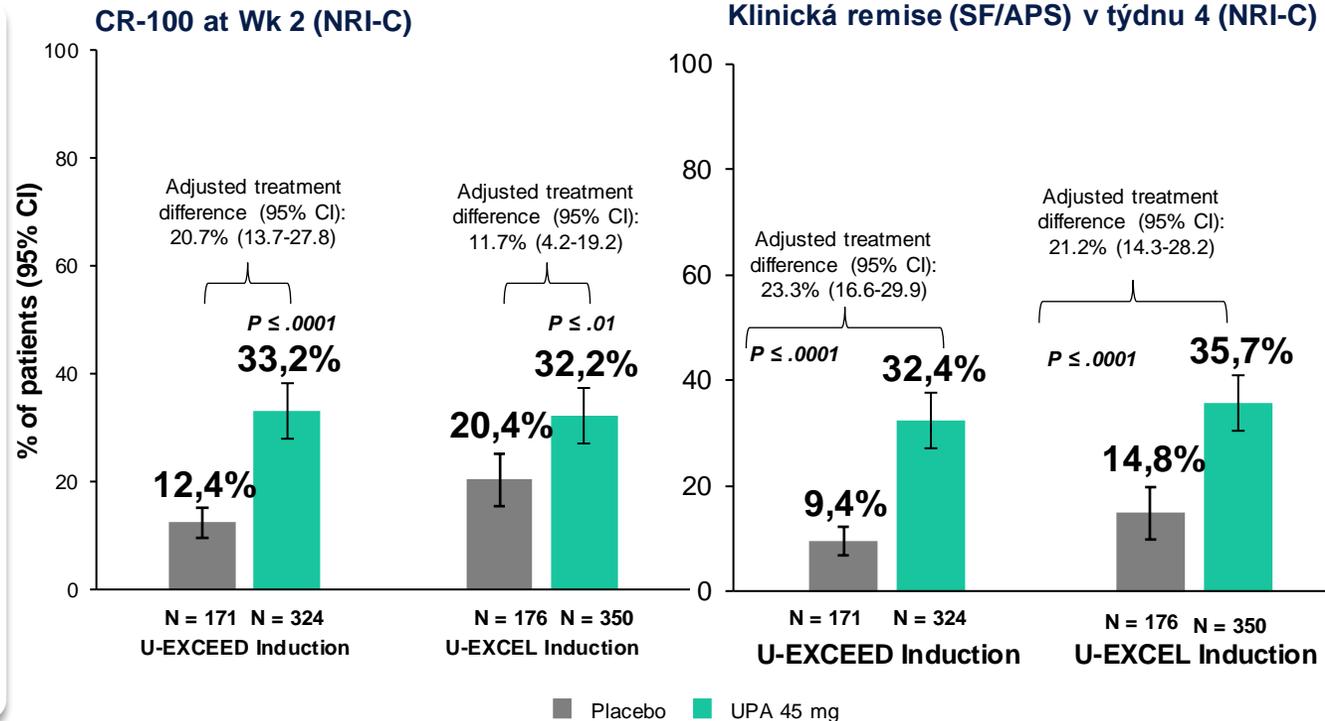
* p < 0.001 vs placebo

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

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

Crohn's disease

Week 2 CR-100 and clinical remission (SF/APS) at Week 4

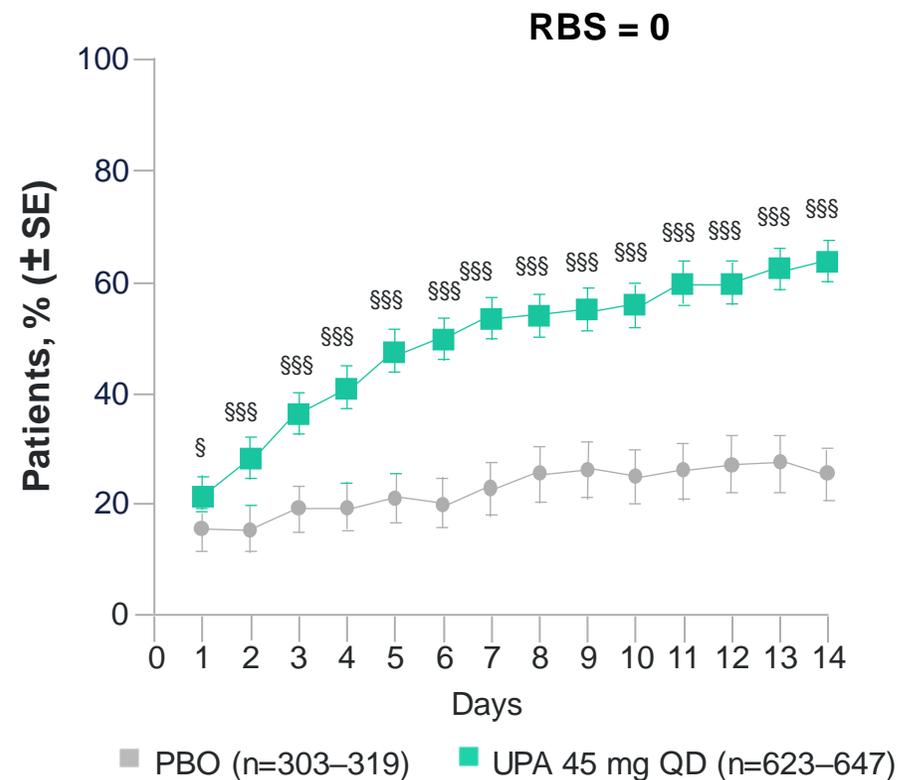
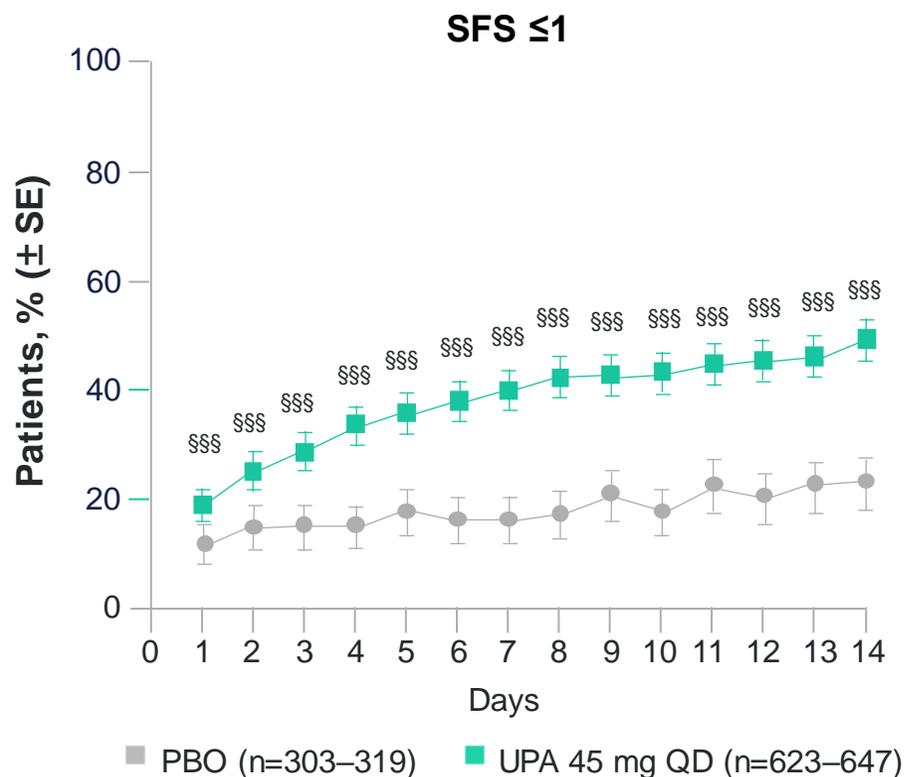


CR-100: decrease of at least 100 points in CDAI from BL

Clinical remission (SF/APS): average daily SF ≤ 2.8 and not worse than BL AND average daily APS ≤ 1 and not worse than BL

Denní průběh dosažení SFS ≤1 a RBS = 0

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

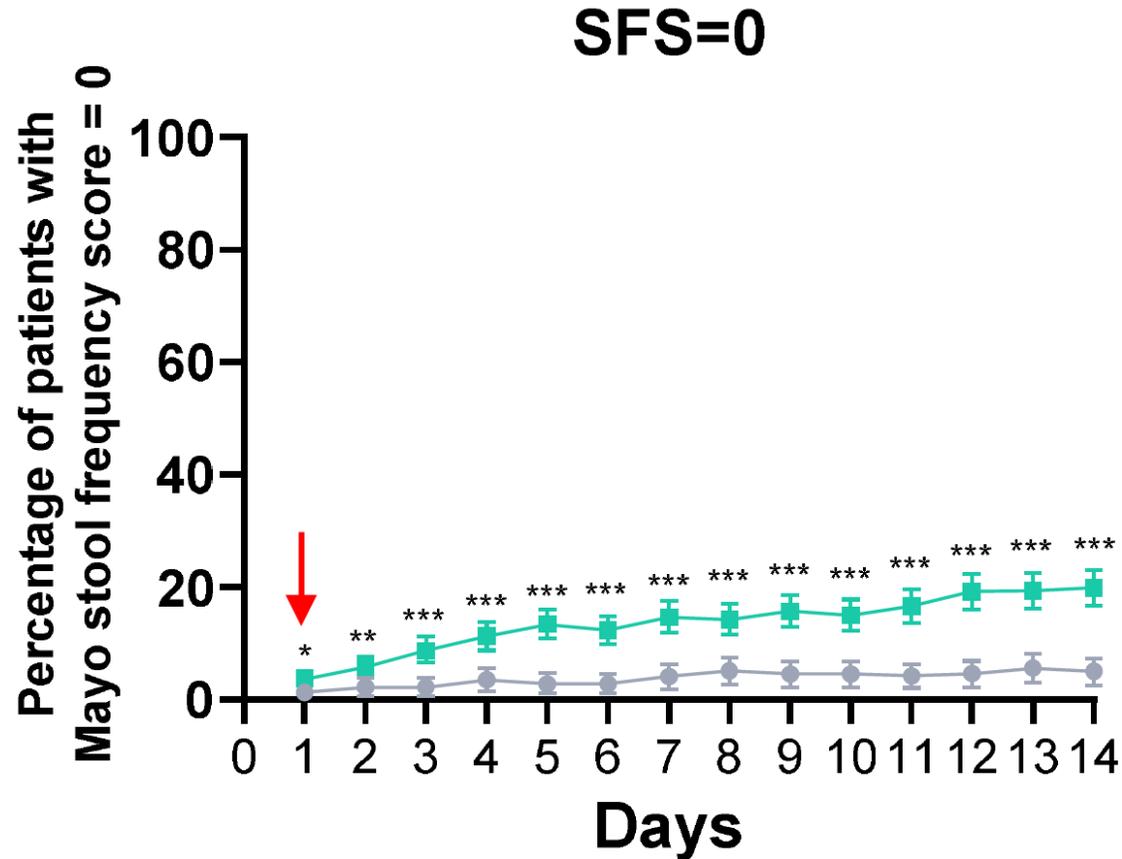


Error bars are ± SE. §Nominal p≤0.05; §§§nominal p≤0.001 vs PBO. P-values are nominal and not multiplicity controlled.² Limitations: Post-hoc analyses lack multiplicity control. No statistical or clinical conclusions can be drawn. PBO, placebo; QD, once daily; RBS, rectal bleeding subscore; SE, standard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

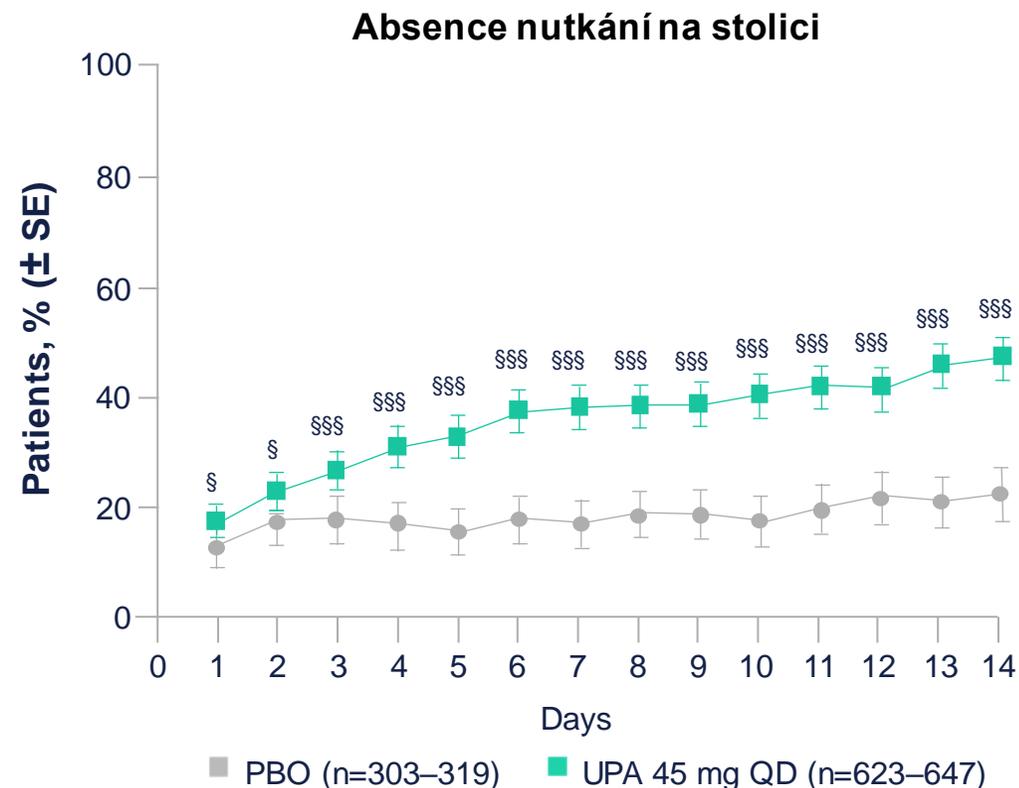
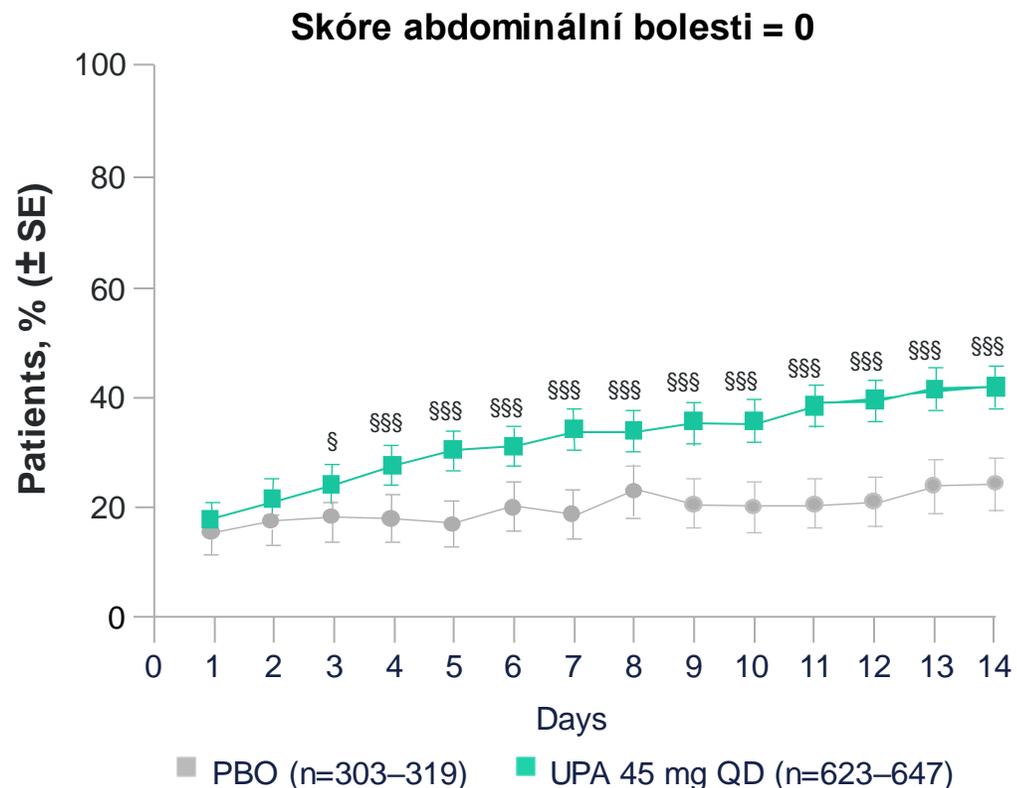
Post-hoc analýza: Pooled analýza U-ACHIEVE a U-ACCOMPLISH
 Symptomatická úleva (SFS = 0) od dne 1 do dne 14



95% CI for adjusted difference and p-value are calculated according to the Cochran-Mantel-Haenszel (CMH) test adjusted for strata. Day 0 represents the first day of randomization and first dose of treatment of induction phase. Patient numbers for all parameters and timepoints were N=303-319 PBO and N=616-634 UPA 45 mg QD. Error bars are \pm standard error. * $P \leq .05$. ** $P \leq .01$. *** $P \leq .001$ vs PBO.

Abdominální bolest = 0 a absence nutkání na stolicí

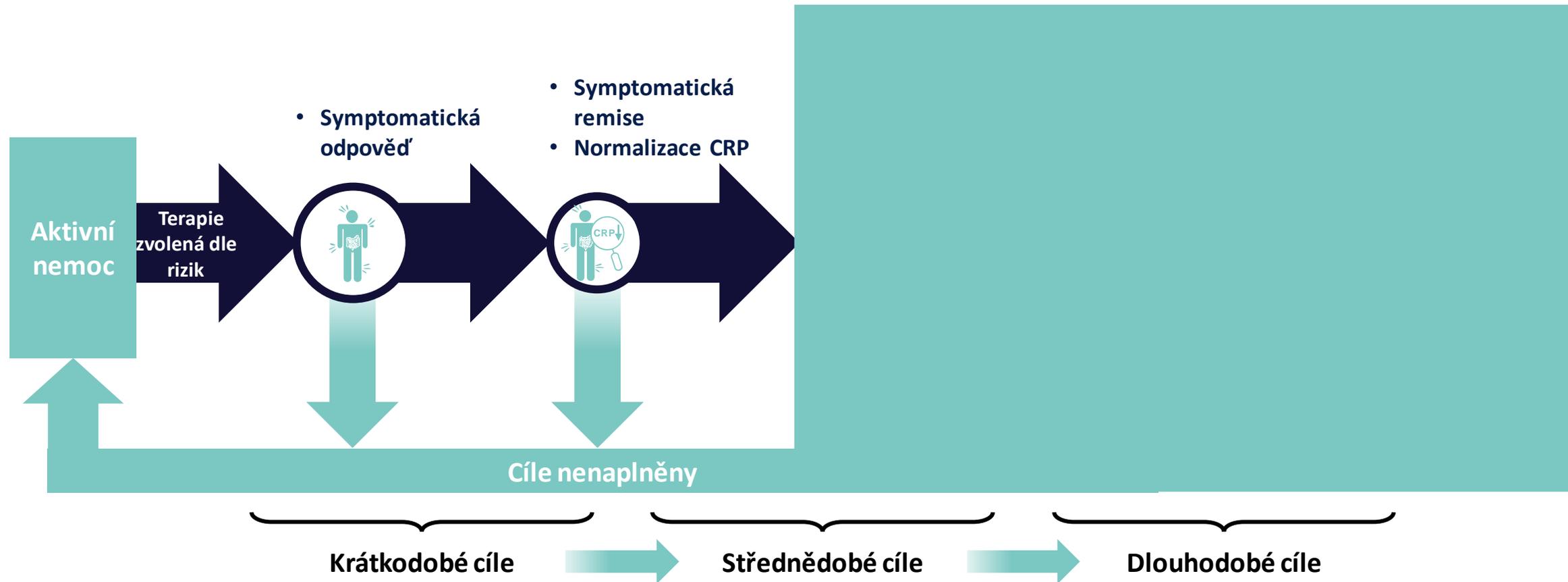
Post-hoc analýza: Pooled analýza U-ACHIEVE a U-ACCOMPLISH
Symptomatická úleva (abdominální bolest = 0 a absence nutkání na stolicí) ode dne 1 do dne 14



Error bars are \pm SE. ^sNominal $p \leq 0.05$; ^{\$\$\$}nominal $p \leq 0.001$ 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).

Treat-to-target přístup se však dále posouvá



^aReferred to as “mucosal healing” in some publications

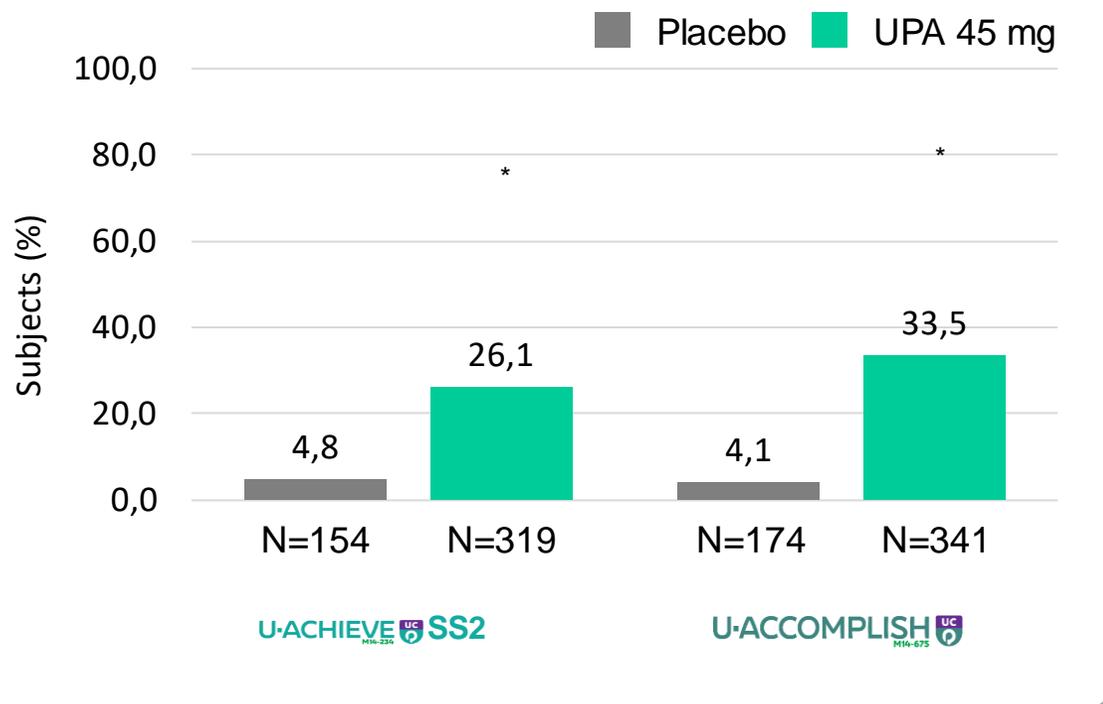
CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis

Requested copyright permission for Figure 2 in Turner D, et al. *Gastroenterology* 2021. Turner D, et al. *Gastroenterology* 2021;160:1570–83

Symptomatic remission and CRP normalization

Ulcerózní kolitida

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 .

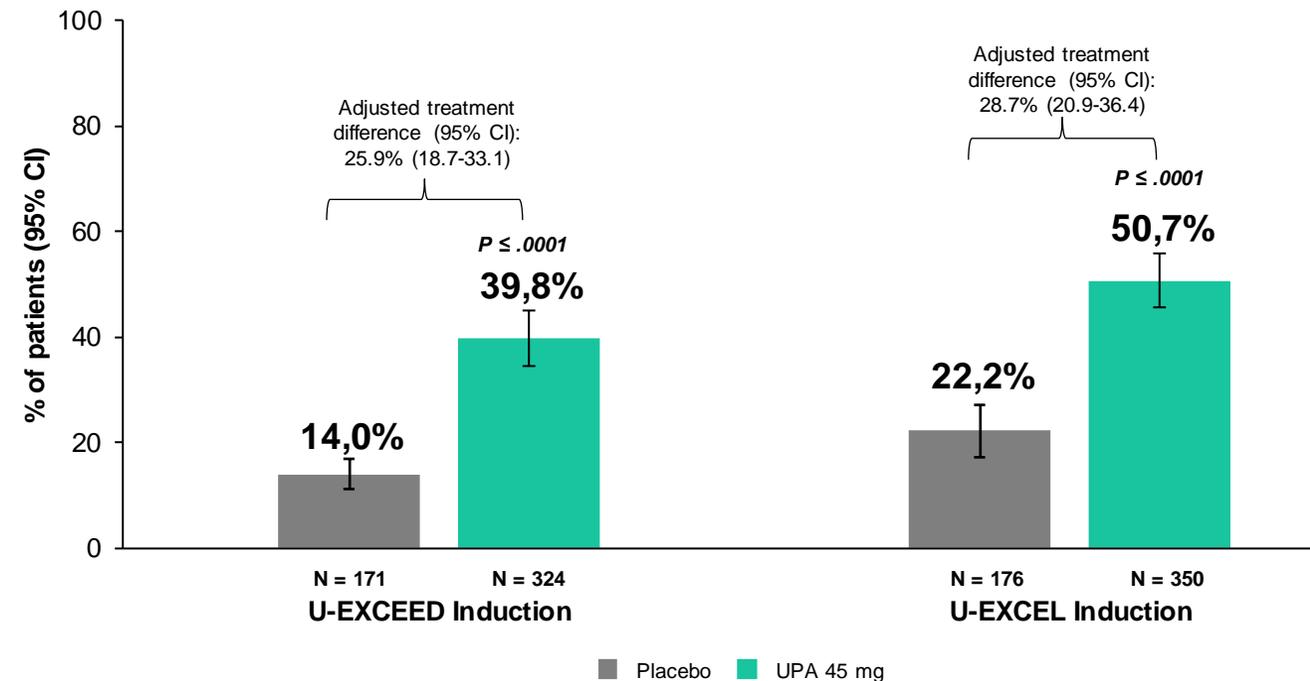
ES, endoscopic subscore; QD, once daily; RBS, rectal bleeding subscore; SFS, stool frequency subscore; UPA, upadacitinib.

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.

Crohnova choroba

Klinická remise (SF/APS) v týdnu 12



Clinical remission (SF/APS): average daily SF ≤ 2.8 and not worse than BL AND average daily APS ≤ 1 and not worse than BL

Symptomatic remission and CRP normalization

Ulcerative colitis

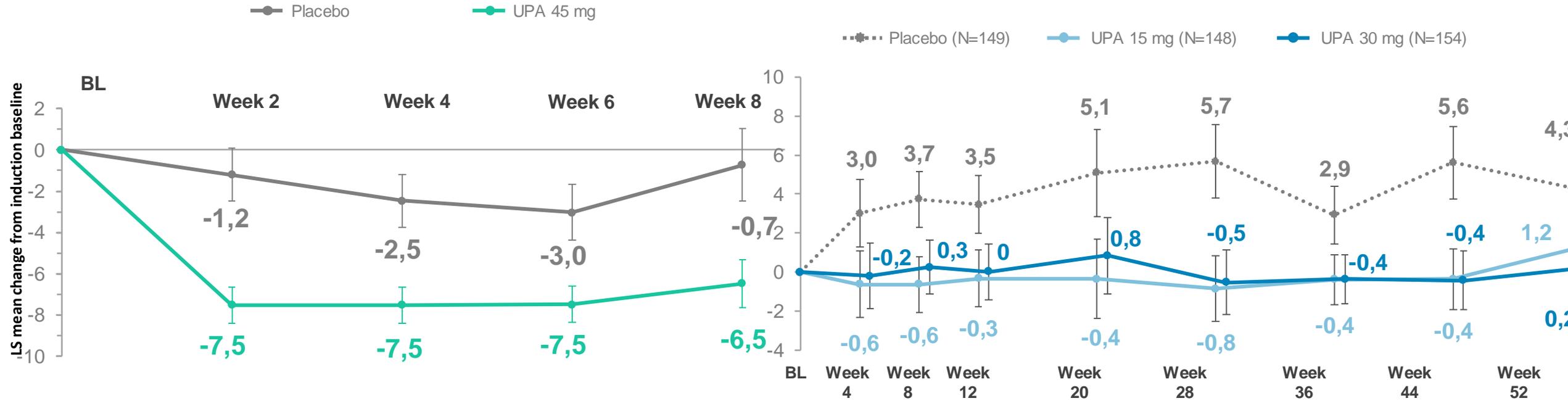
Změny hladiny CRP v indukční fázi



Změna hladin CRP v udržovací fázi



High-sensitivity C-reactive Protein (mg/L) Change From Baseline (MMRM)



Symptomatic remission and normalization of CRP

Crohnova choroba

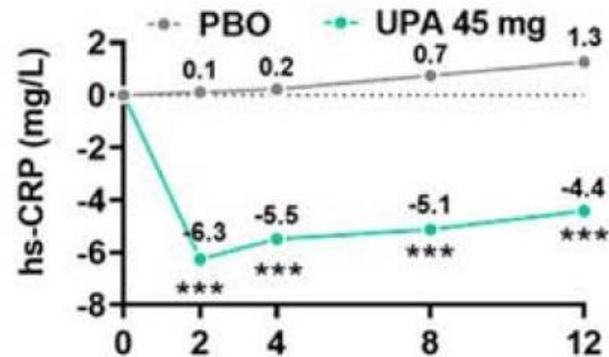
Změny hladiny CRP v indukční fázi (medián)



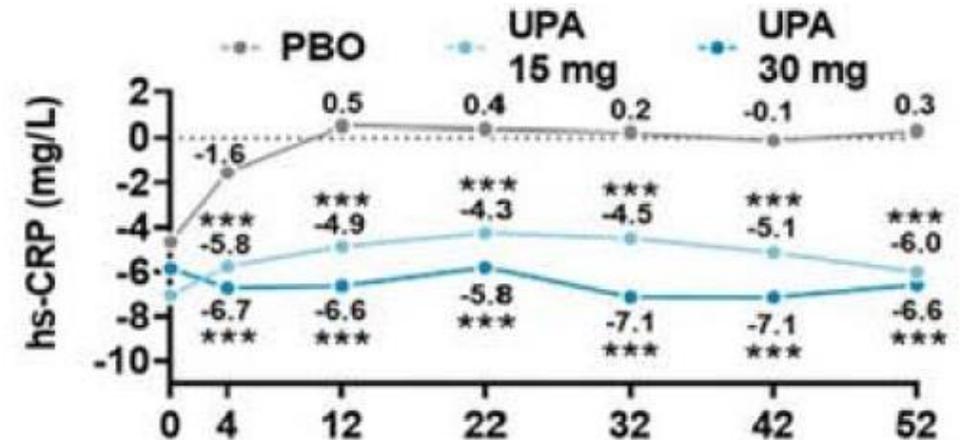
Median (range)
BL hs-CRP (mg/L)

PBO:
7.9 (0.2–126.0)

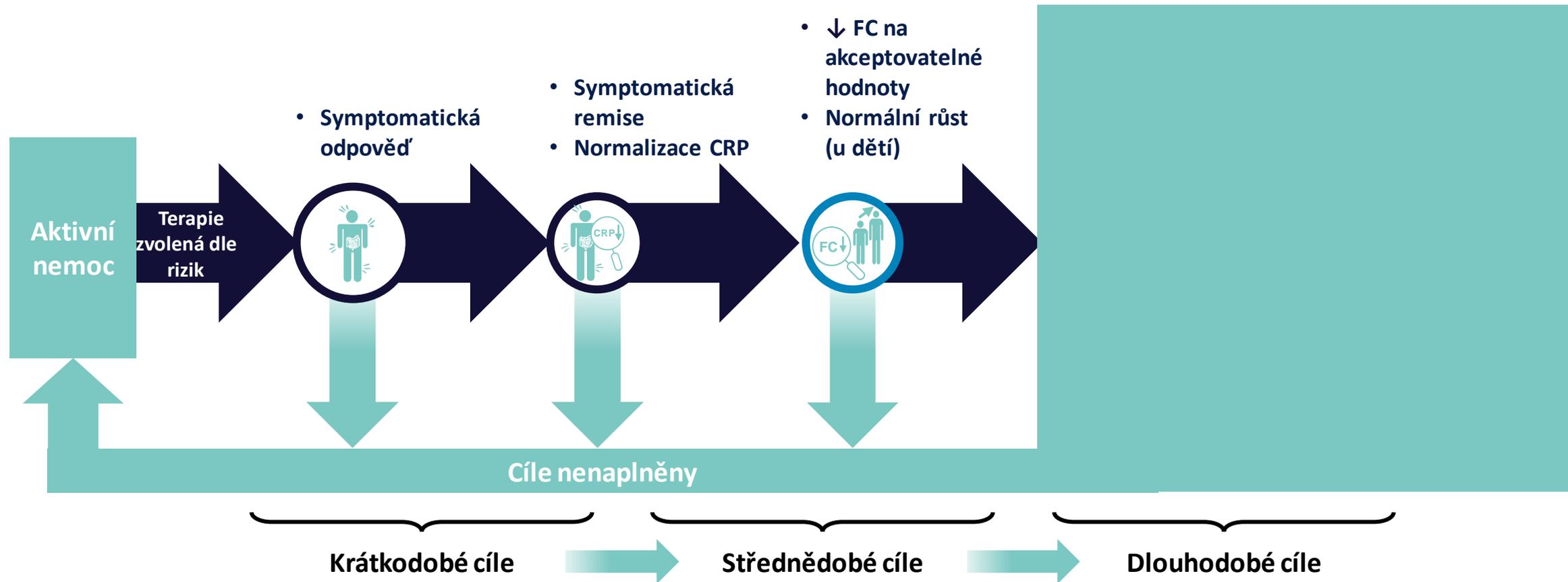
UPA 45 mg:
8.8 (0.2–144.0)



Změna hladin CRP v udržovací fázi (medián)



Treat-to-target přístup se však dále posouvá



^aReferred 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

Requested copyright permission for Figure 2 in Turner D, et al. *Gastroenterology* 2021. Turner D, et al. *Gastroenterology* 2021;160:1570–83

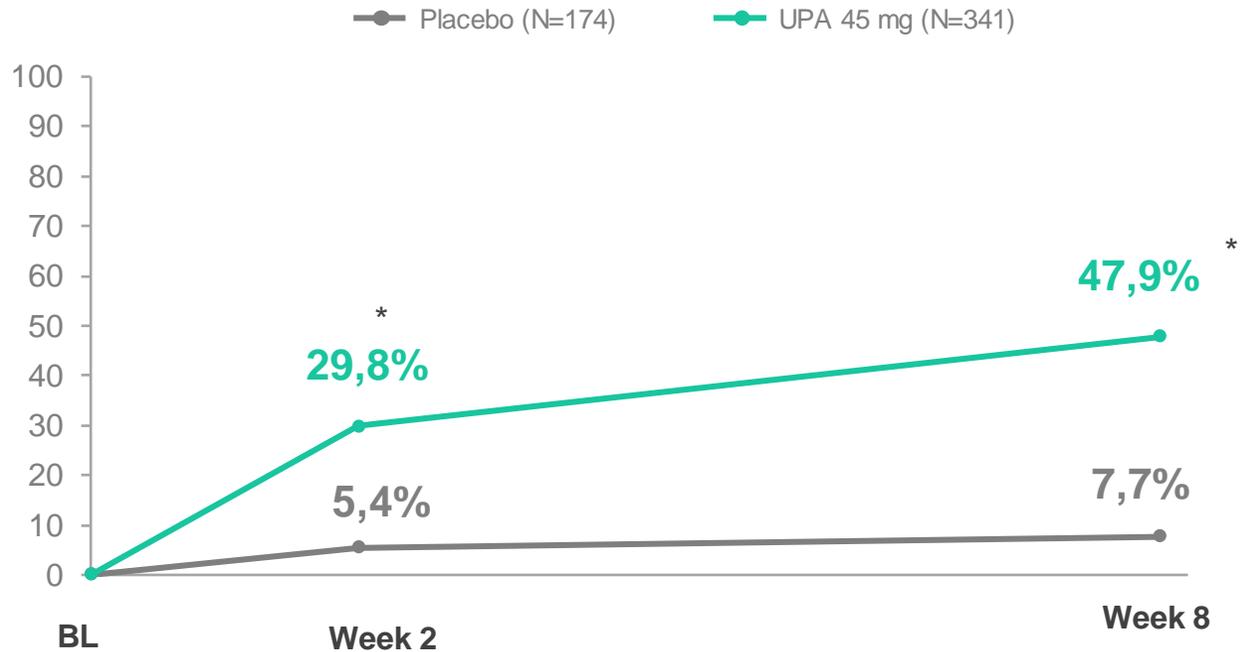
Snížení hladiny fekálního kalprotektinu

Ulcerózní kolitida

Hladiny fekálního kalprotektinu v indukci



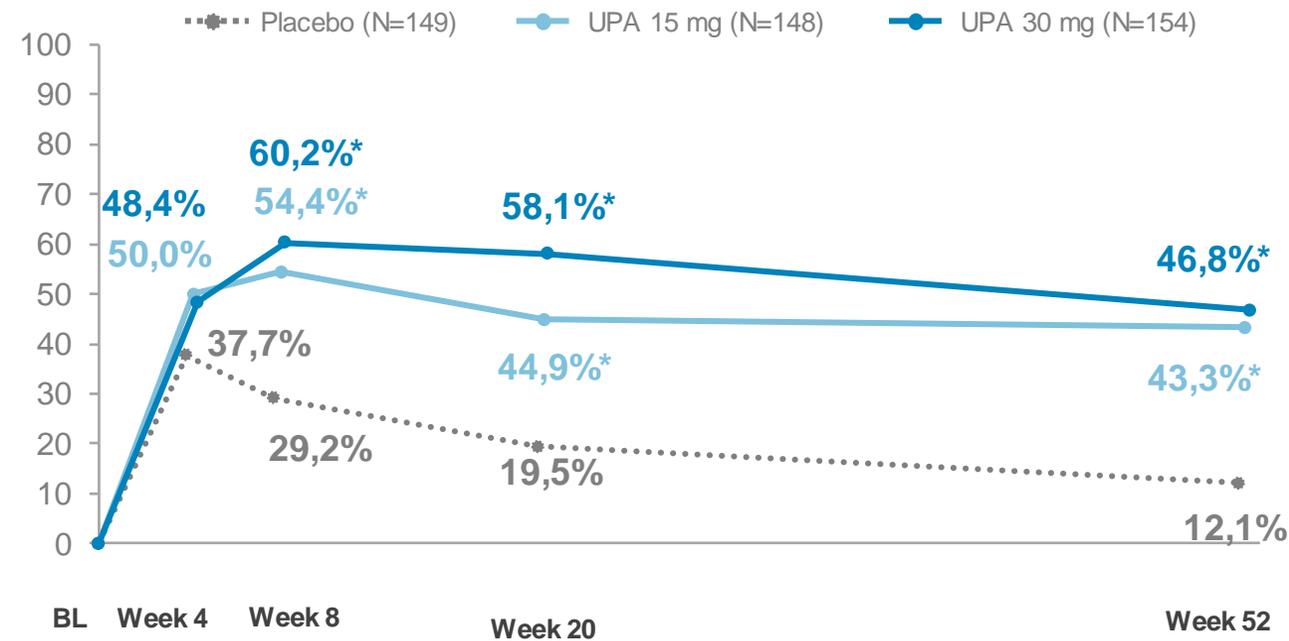
Proportion of Patients Achieving Fecal Calprotectin <150 mg/kg up to 8 Weeks



Hladiny fekálního kalprotektinu v udržovací fázi



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

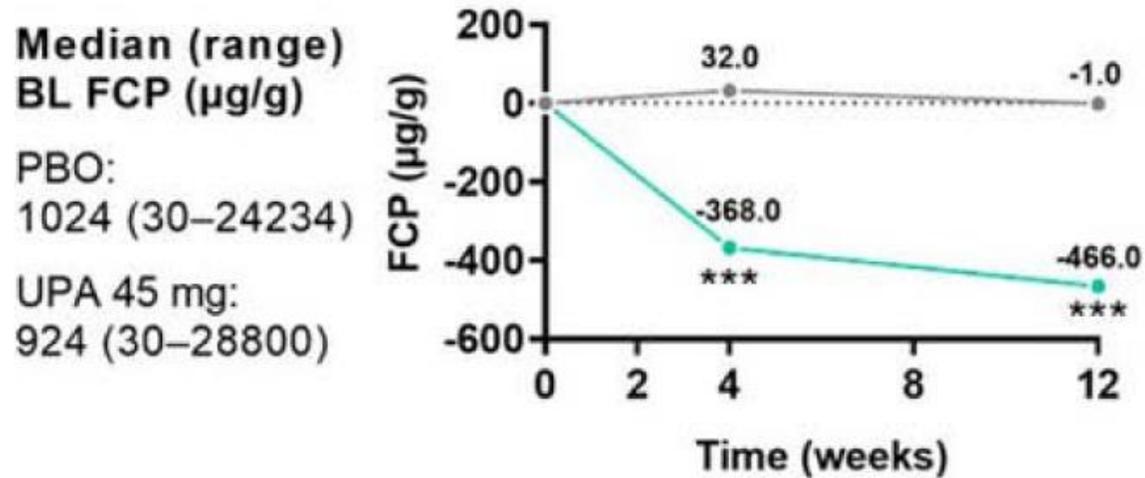


*P values of P<0.001 are nominal and cannot be considered for statistical significance.
BL, baseline; Fcal, fecal calprotectin; hs-CRP, high-sensitivity C-reactive protein; UPA, upadacitinib.
1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128.

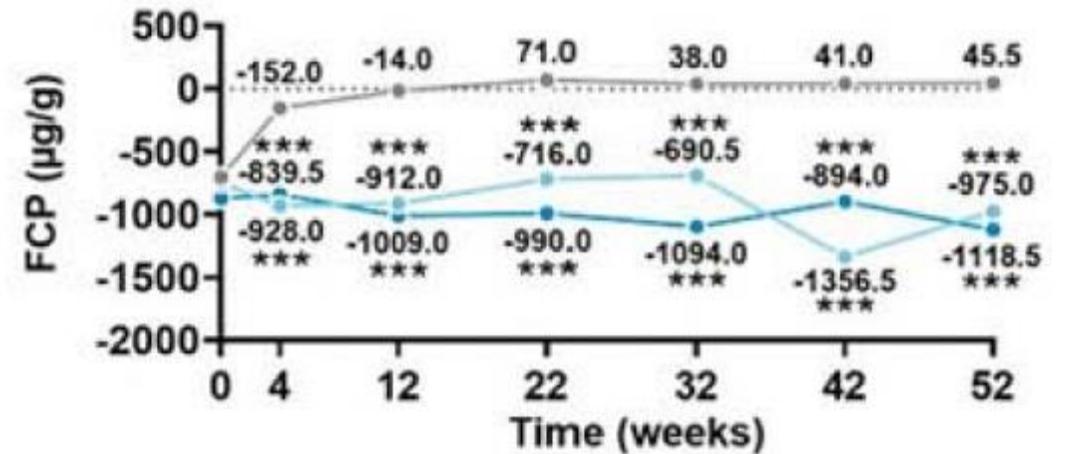
Snížení hladiny fekálního kalprotektinu

Crohnova choroba

Změna hladiny fekálního kalprotektinu v indukční fázi (medián)

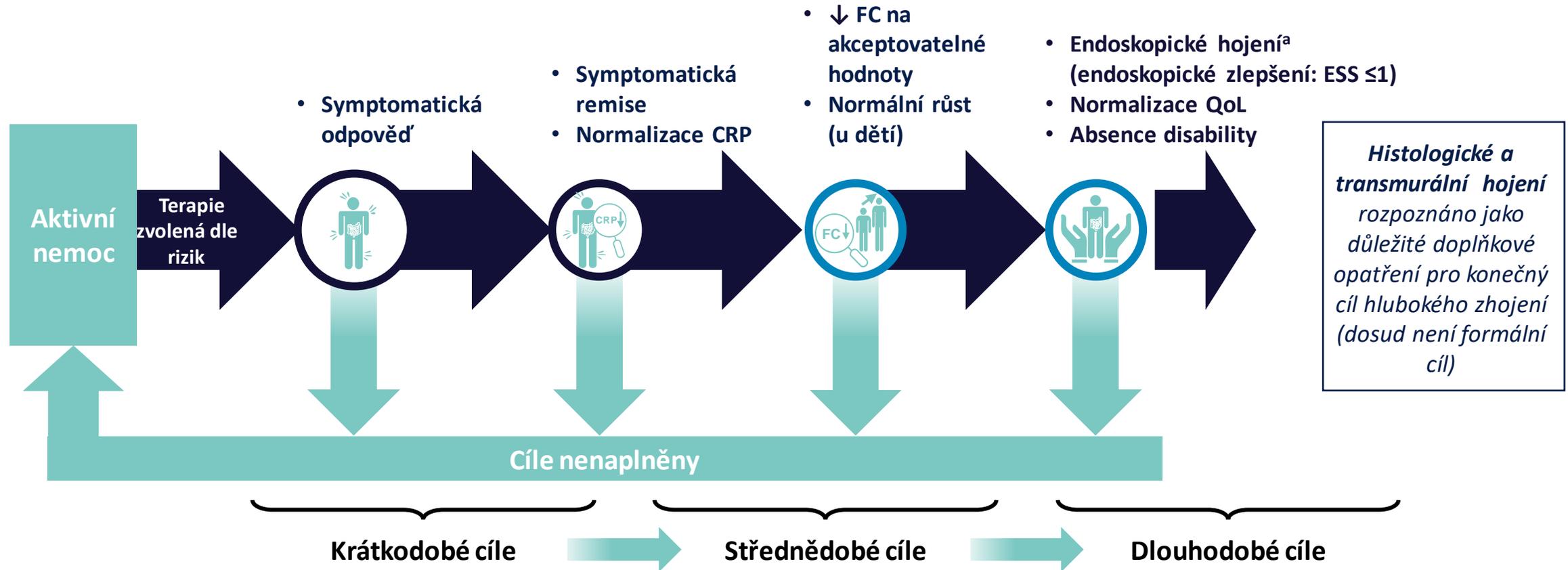


Změna hladiny fekálního kalprotektinu v udržovací fázi (medián)



Treat-to-target přístup se však dále posouvá

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.



^aReferred to as "mucosal healing" in some publications

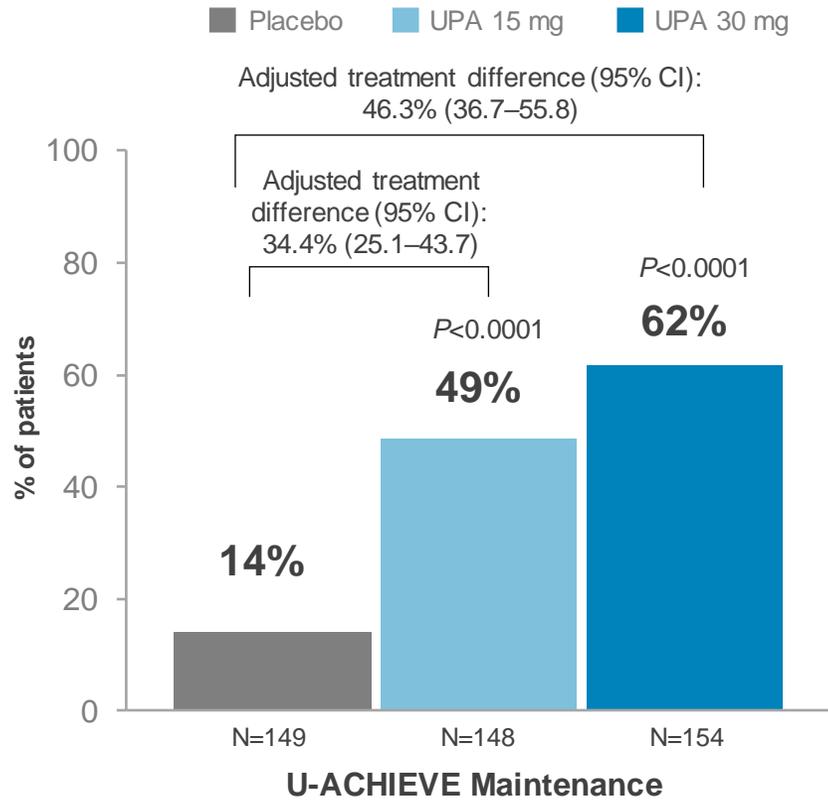
CRP, C-reactive protein; ESS, endoscopic subscore; FC, fecal calprotectin; QoL, quality of life; STRIDE, Selecting Therapeutic Targets in Inflammatory Bowel Disease; UC, ulcerative colitis

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Endoskopické hojení

Ulcerózní kolitida

Endoskopické zlepšení (ESS≤1) v týdnu 52

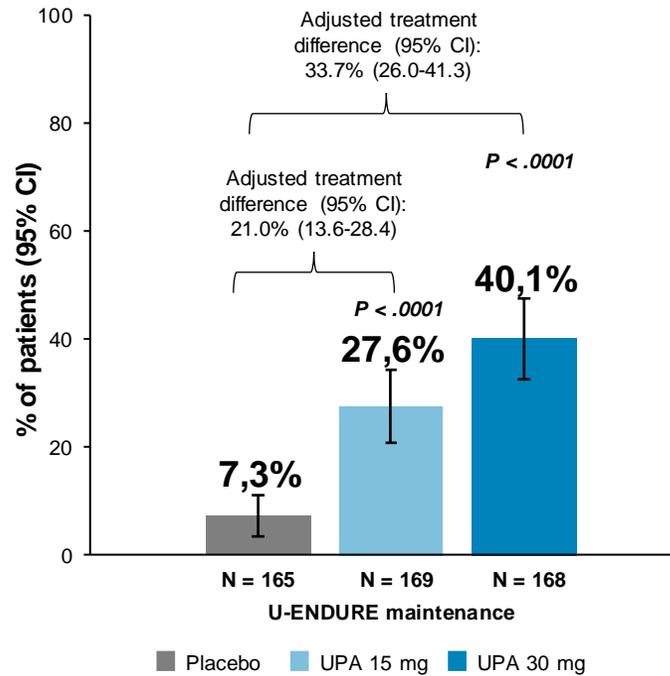


Crohnova choroba

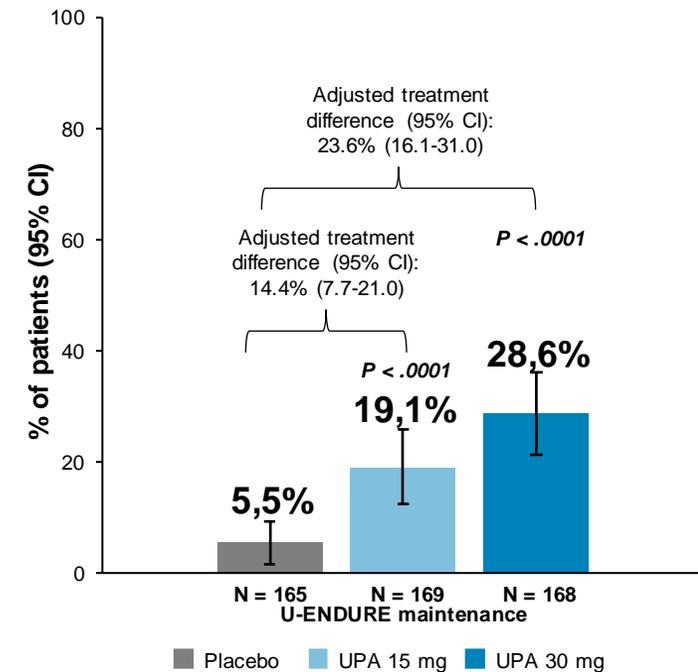
Endoskopická odpověď a remise v týdnu 52



Endoscopic Response at Wk 52 (NRI-C)



Endoscopic Remission at Wk 52 (NRI-C)



Endoscopic response: decrease in SES-CD >50% from baseline (BL) (or for patients with a BL SES-CD of 4, at least a 2-point reduction from BL), as scored by central reviewer

Endoscopic remission: SES-CD ≤ 4 and at least a 2-point reduction versus BL and no subscore greater than 1 in any individual variable, as scored by a central reviewer

CI, confidence interval; UPA, upadacitinib.

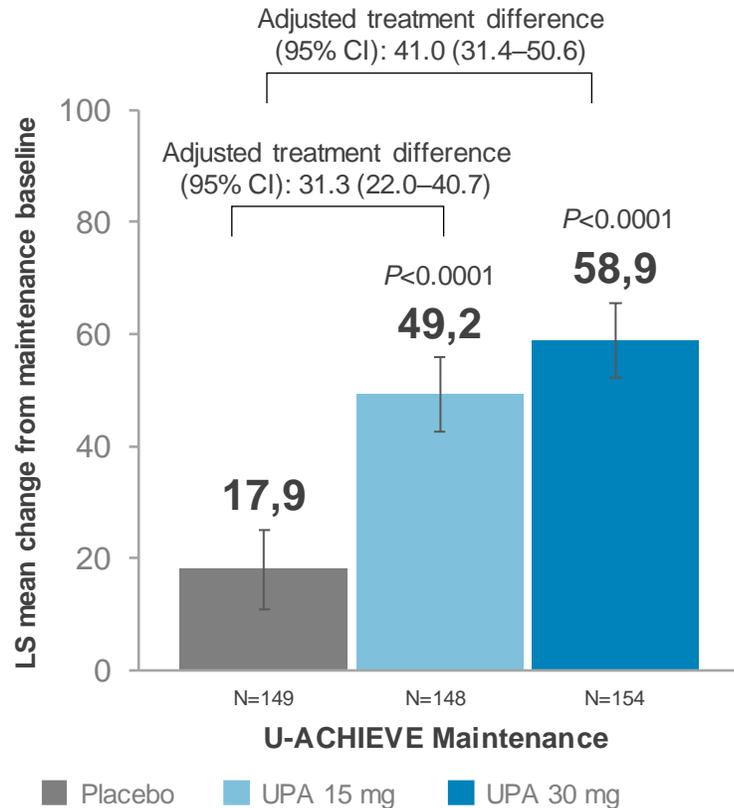
1. Danese S et al. *Lancet*. 2022;399(10341):2113-2128.

APS, abdominal pain score; BL, baseline; CDAI, Crohn's Disease Activity Index; CI, confidence interval; COVID-19, coronavirus disease 2019; NRI-C, nonresponder imputation–COVID-19; SES-CD, Simple Endoscopic Score in Crohn's Disease; SF, stool frequency; UPA, upadacitinib; wk, week. 1. Colombel JF, et al. *Gastroenterology*. 2022;162(7):S-1394. 2. Loftus EV Jr, et al. *United European Gastroenterol J*. 2022;10(S8):103-104. 3. Panes J, et al. Oral presentation at: the American College of Gastroenterology Annual Scientific Meeting; October 21-26, 2022; Charlotte, NC.

Normalizace kvality života

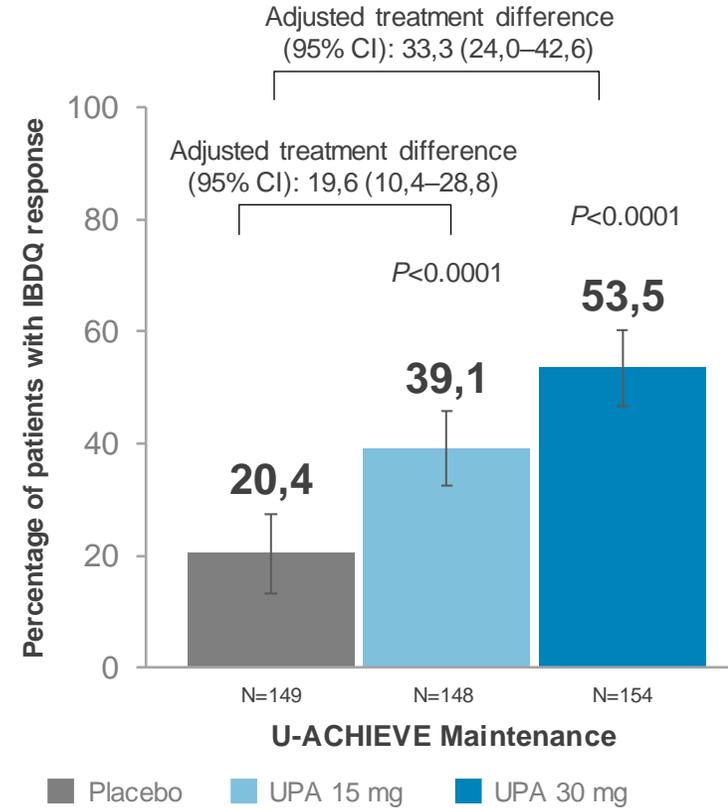
Ulcerózní kolitida

Změna od baseline v IBDQ v týdnu 52



Crohnova choroba

Procento pacientů s IBDQ odpovědí 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.

Histologické hojení u ulcerózní kolitidy: histologicko-endoskopické slizniční zlepšení

HEMI v týdnu 8

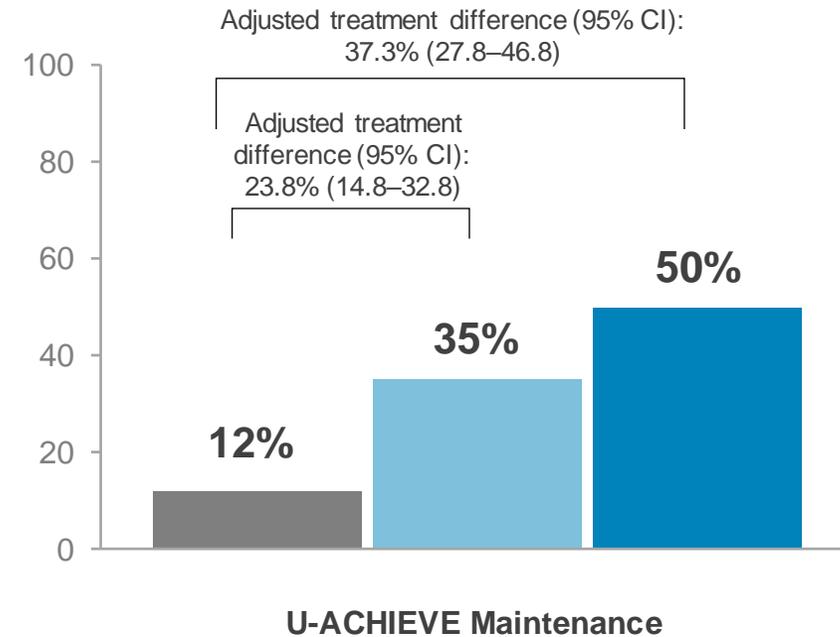
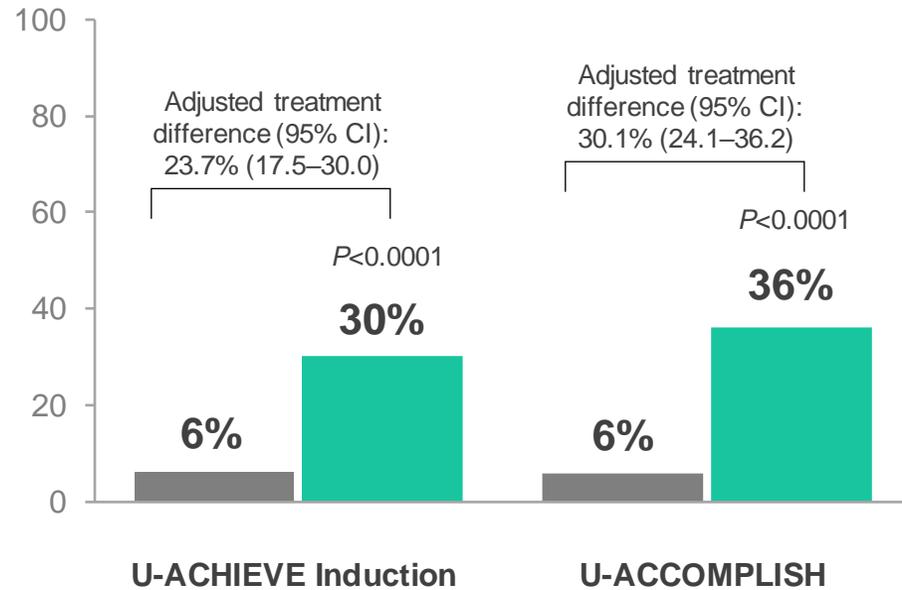


HEMI v týdnu 52



■ Placebo ■ UPA 45 mg

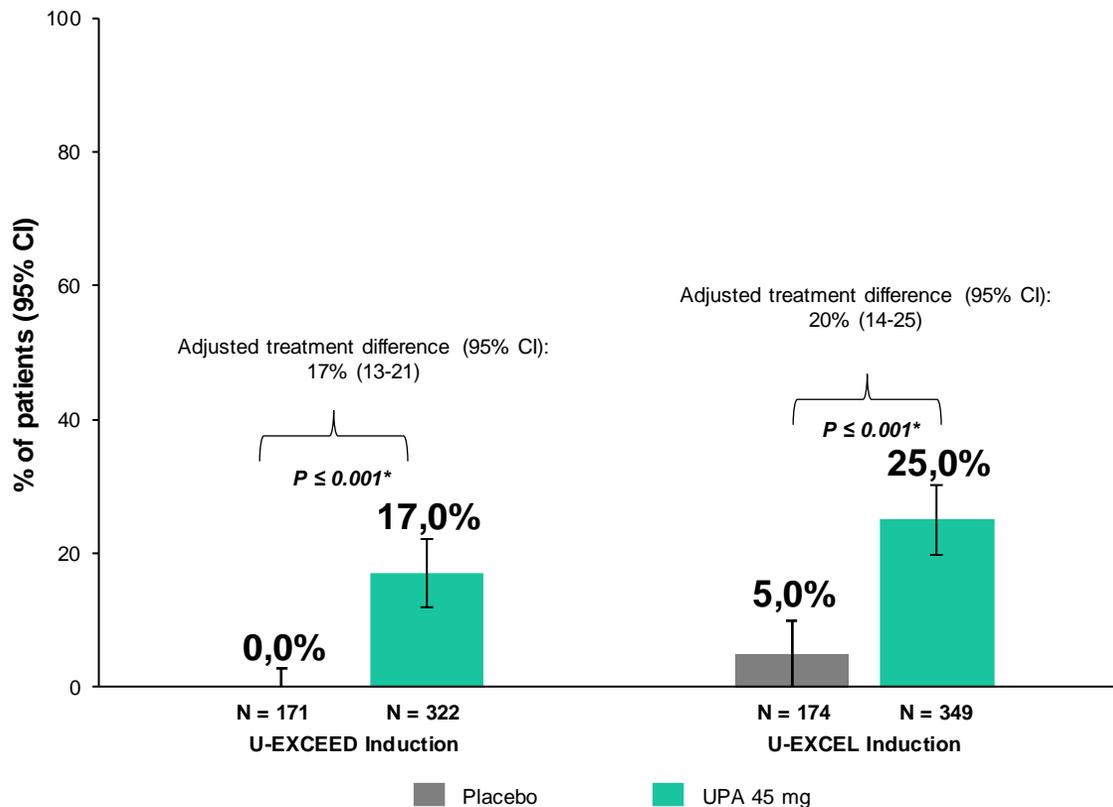
■ Placebo ■ UPA 15 mg ■ UPA 30 mg



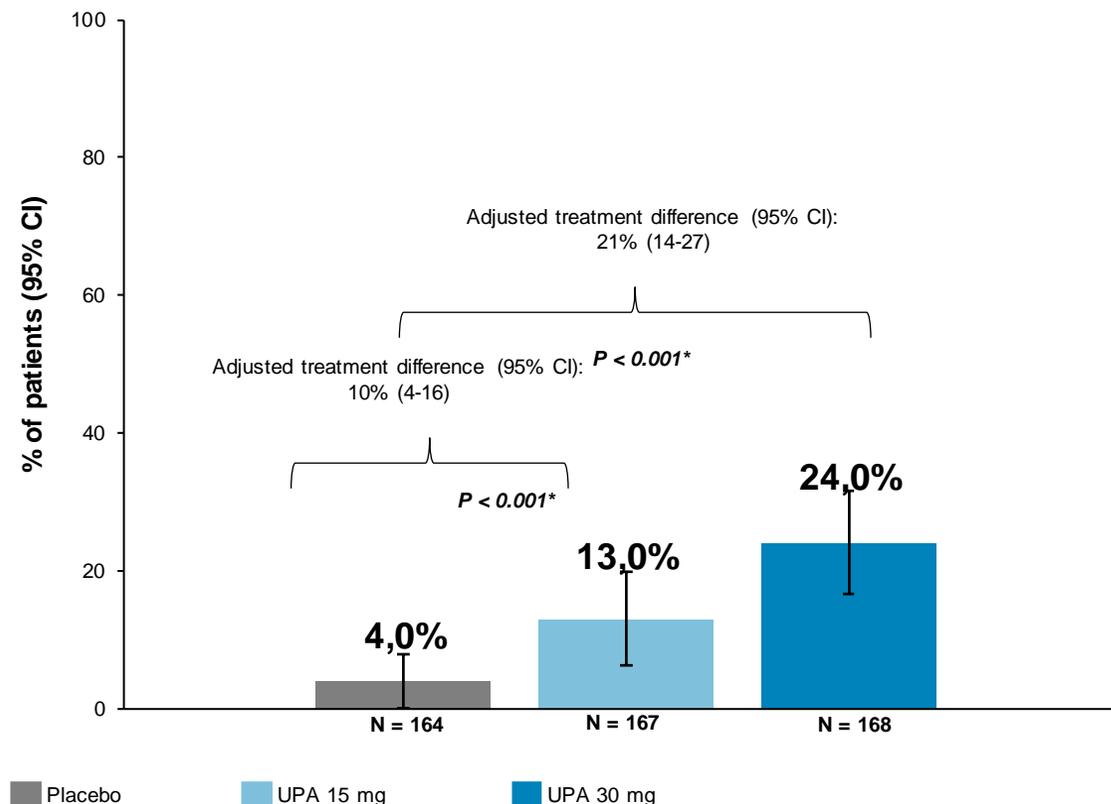
Geboes \leq 3.1: neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue²

Slizniční hojení u Crohnovy choroby

SES-CD subskóre ulcerovaného povrchu 0 v týdnu 12



SES-CD subskóre ulcerovaného povrchu 0 v týdnu 52



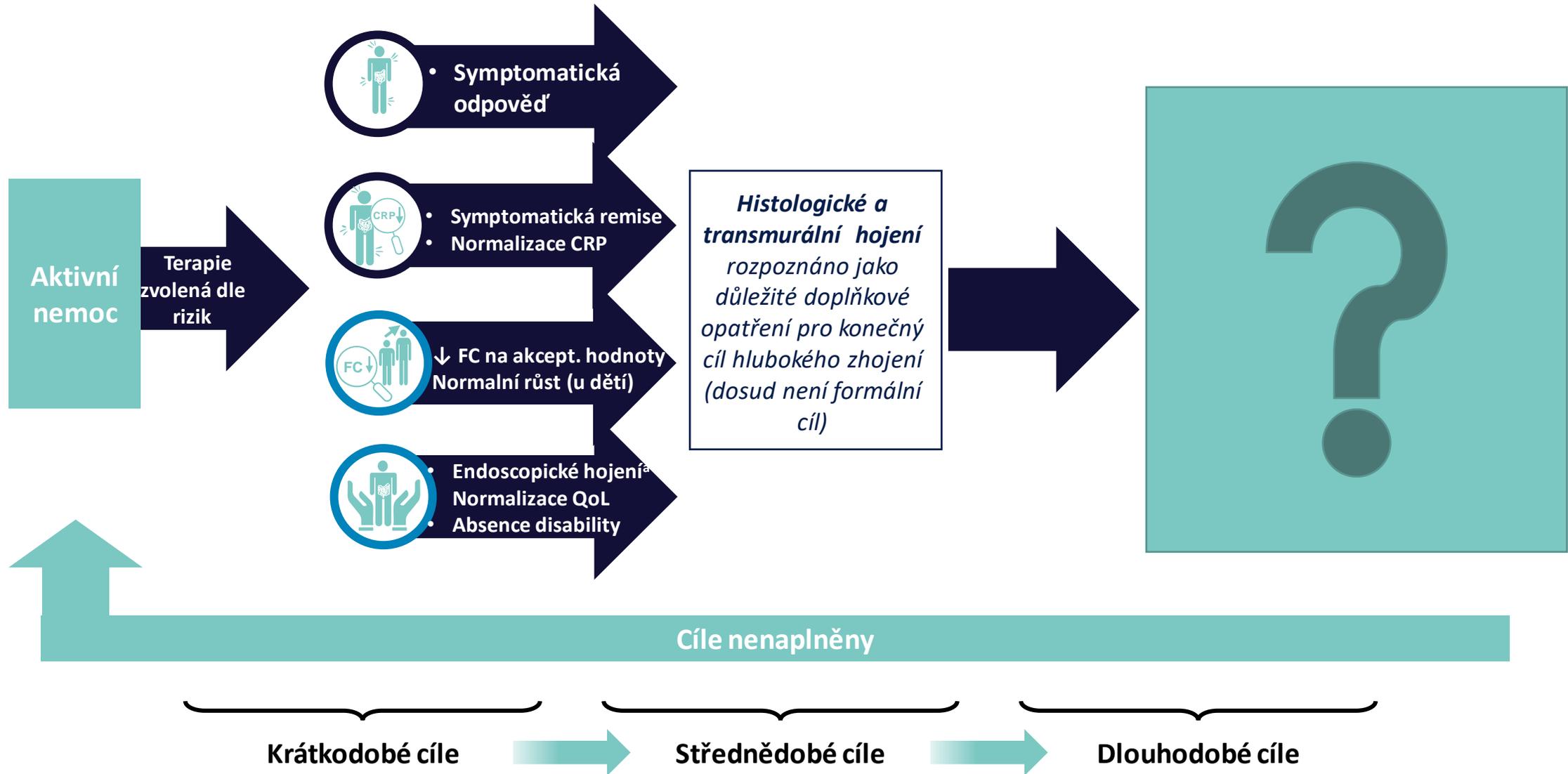
Mucosal Healing: SES-CD ulcerated-surface subscore of 0 in patients with SES-CD ulcerated-surface subscore ≥ 1 at BL

*nominal p value

APS, abdominal pain score; BL, baseline; CI, confidence interval; COVID-19, coronavirus disease 2019; NRI-C, nonresponder imputation-COVID-19; SES-CD, Simple Endoscopic Score in Crohn's Disease; SF, stool frequency; UPA, upadacitinib; wk, week.

1. Upadacitinib SmPC

Treat-to-target přístup s upadacitinibem?



^aReferred 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

Treat-to-target koncept v klinické praxi

Real World Implementation of Treat-to-Target in Patients with IBD in a Learning Health System: An IBD Qorus Collaborative Study

Siddharth Singh, Brant J. Oliver, Jason K. Hou, Donald Lum, Welmoed K. van Deen, S. Alandra Weaver, Corey A. Siegel, Gil Y. Melmed, on behalf of IBD Qorus

Digestive Disease Week
Chicago, IL
May 9, 2023

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 $\geq 2\%$ 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



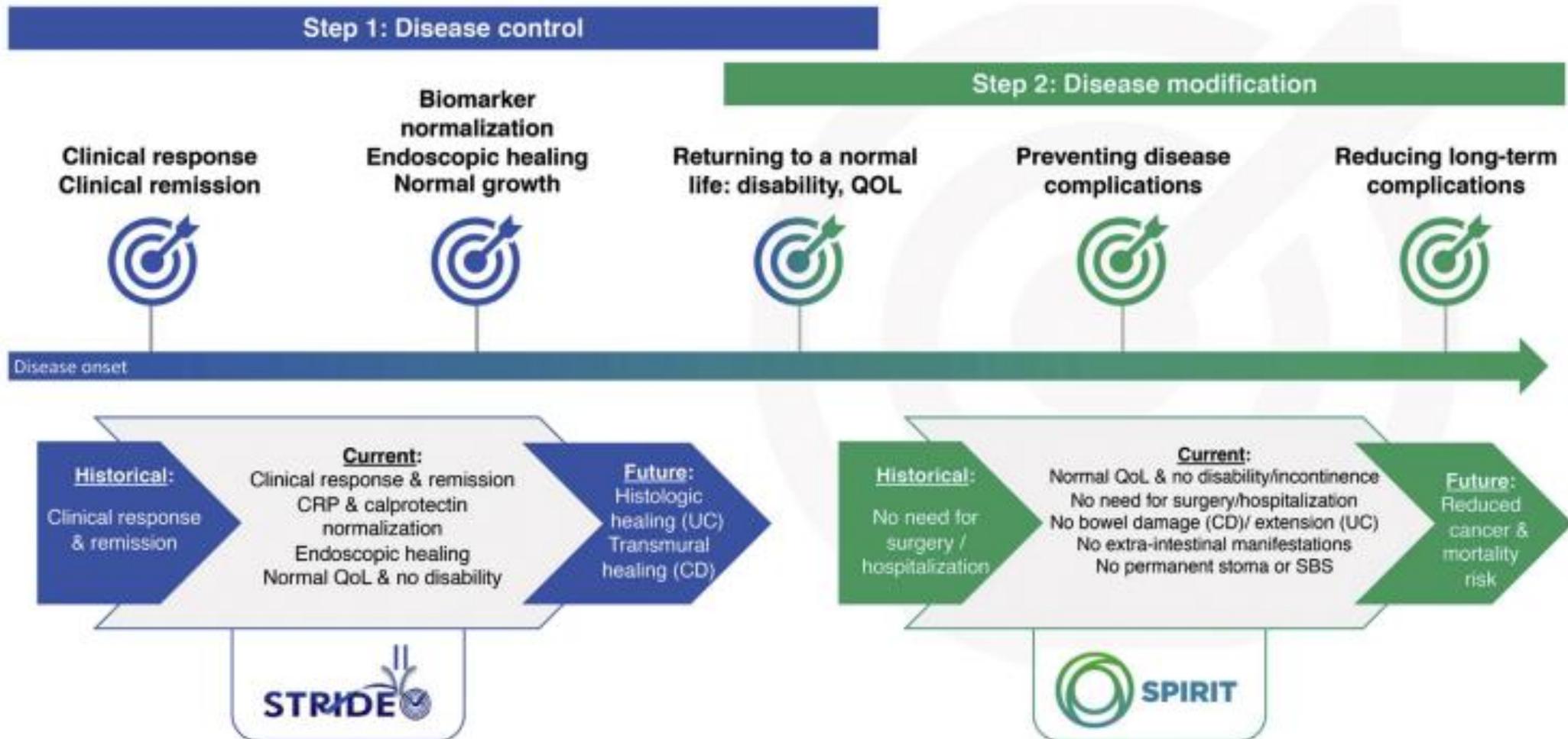
Treat-to-target koncept v klinické praxi

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



SPIRIT: Selecting End Points foR Disease-ModificatIon Trials

Od terapeutických cílů k chorobu modifikující léčbě



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**