ONLINE SUPPLEMENT

AGA LIVING CLINICAL PRACTICE GUIDELINE ON THE PHARMACOLOGIC MANAGEMENT OF MODERATE-TO-SEVERE CROHN'S DISEASE

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eFigure 13: Forest plot summarizing (A) comparative remission rates and (B) comparative disease complication rates at 1 year for early combined immunosuppression compared to conventional step up therapy efficacy in patients with moderately to severely active Crohn's disease in steroid-free remission on combination therapy

eTable 1: Conflicts of interest for the guideline panel members

This table to be inserted at publication.

eTable 2: Search strategy for key focus areas addressed in the guidelines

Databases: MEDLINE ALL (Ovid, 1946 to August 14, 2024), Embase (Ovid, 1996 to August 14, 2024); Cochrane CENTRAL (Ovid, Inception to July 2024).

1. Crohn Disease/ use medall,cctr
2. exp Crohn disease/ use oemezd
3. Crohn*.ti,ab,kw,kf,af.
4. ((Inflammatory bowel disease* or IBD) not (ulcerative colitis or UC)).ti.
5. or/1-4 [CD]
6. exp Tumor Necrosis Factor Inhibitors/ use medall,cctr
7. exp tumor necrosis factor antibody/ use oemezd
8. exp Receptors, Tumor Necrosis Factor/ use medall,cctr
9. exp Tumor Necrosis Factors/ use medall,cctr
10. tumor necrosis factor/ use oemezd
11. tumor necrosis factor receptor/ use oemezd
12. ((tumor necrosis or tumour necrosis or TNF or antitumor necrosis or antitumour necrosis or antiTNF* or Cachectin) adj2 (factor* or inhibit* or antibod* or antagonist* or block* or biologic*)).ti,ab,kw,kf.
13. exp Antibodies, Monoclonal/ use medall,cctr
14. exp monoclonal antibody/ use oemezd,medall,cctr
15. (monoclonal adj2 antibod*).ti,ab,kw,kf.
16. (Infliximab or "ABP 710" or ABP710 or Avakine or Avsola or cA2 or Flixabi or "GP 1111" or GP1111 or IFX or Inflectra or INFLIX or Ixifi or "PF 06438179" or "PF 6438179" or PF06438179 or PF6438179 or Remicade or Remsima or Renflexis or Revellex or "TA 650" or TA650 or Zessly or "MAb cA2" or "170277-31-3").ti,ab,kw,kf,rn.
17. (Adalimumab or Humira or Amjevita or Cyltezo or "D2E7 Antibody" or Trudexa or "abp 501" or abp501 or "abt d2e7" or abtd2e7 or adaly or amgevita or "avt 02" or avt02 or "bat 1406" or bat1406 or "bax 2923" or "bax 923" or bax2923 or bax923 or "bi 695501" or bi695501 or "chs 1420" or chs1420 or "ct p17" or ctp17 or "da 3113" or da3113 or "dmb 3113" or dmb3113 or exemptia or "fkb 327" or fkb327 or fyzoclad or "gp 2017" or gp2017 or hadlima or halimatoz or hefiya or "hlx 03" or hlx03 or hulio or hyrimoz or "ibi 303" or ibi303 or idacio or imraldi or kromeya or "lu 200134" or lu200134 or "m 923" or m923 or mabura or "msb 11022" or msb11022 or "ons 3010" or ons3010 or "pf 06410293" or "pf 6410293" or pf06410293 or pf6410293 or raheara or "sb 5" or sb5 or solymbic or "zrc 3197" or zrc3197 or "1446410-95-2" or "331731-18-1").ti,ab,kw,kf,rn.
18. (Certolizumab or "cdp 870" or cdp870 or cimzia or "pha 738144" or pha738144 or "428863-50-7").ti,ab,kw,kf,rn.
19. (Vedolizumab or anti alpha 4* or antialpha 4* or Entyvio or kynteles or "idp 02" or idp02 or "MLN 02" or mln02 or "MLN-0002" or MLN0002 or "pb 016" or pb016 or ro7246311 or "ro 7246311").ti,ab,kw,kf,rn.
20. (Natalizumab or "an 10022" or "an 100226" or an10022 or "an100226" or antegran or antegren or "bg 0002" or bg0002 or "dst 356a1" or dst356a1 or "pb 006" or pb006 or "pbp 2002" or pbp2002 or tyruko or tysabri).ti,ab,kw,kf,rn.
21. (Ustekinumab or "abp 654" or abp654 or "avt 04" or avt04 or "bat 2206" or bat2206 or "bfi 751" or bfi751 or "bmab 1200" or bmab1200 or "bow 090" or bow090 or "cnto 1275"

or cnto1275 or "ct p43" or ctp43 or "dmb 3115" or dmb3115 or "eb 1004" or eb1004 or "fyb 202" or fyb202 or "ons 3040" or ons3040 or "pb 007" or pb007 or "ro 723 3920" or "ro 7233920" or ro7233920 or "sb 17" or sb17 or stelara or stellara).ti,ab,kw,kf,rn.
22. Janus Kinase Inhibitors/ use medall,cctr
23. exp Janus kinase inhibitor/ use oemezd
24. ((JAK or Janus Kinase or Janus tyrosine kinase) adj2 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.
25. (upadacitinib or "abt 494" or abt494 or rinvoq).ti,ab,kw,kf,rn.
26. ((IL-23 or interleukin or cytokine) adj2 (antagonist* or inhibit* or block*)).ti,ab,kw,kf.
27. exp cytokine receptor antagonist/ use oemezd
28. (risankizumab or "abbv 066" or abbv066 or "bi 655066 bi655066" or skyrizi).ti,ab,kw,kf,rn.
29. (mirikizumab or "ly 3074828" or ly3074828 or omvoh).ti,ab,kw,kf,rn.
30. (guselkumab or "cnto 1959" or cnto1959 or tremfya).ti,ab,kw,kf,rn.
31. (mercaptopurine or 6MP or "6-MP" or allmercap or bw 57 323h or bw 57323h or bw57323h or empurine or e7wed276i5 or hanixol or ismipur or leukerin or leupurin* or loulla or medipurin or mercaleukin or mercaptopurine* or mercapurene or mern or mycaptine or nsc 755 or nsc755 or pkk6muz20g or puri nethol or purimmun or purine 6 thiol or purine thiol or purimethol or puri-nethol or purinethiol or purinethol or purixan or thiohypoxanthine or thiopurine* or u 4748 or u4748 or xaluprine).ti,ab,kw,kf,rn.
32. exp Mercaptopurine/ use medall,cctr
33. 6 mercaptopurine derivative/ or mercaptopurine/ use oemezd
34. (azathioprine or arathioprin* or aza-q or azafalk or azafor or azahexal or azamedac or azamun* or azanin or azapin or azapress or azaprine or azarex or azasan or azathiodura or azathiopine or azathioprim or azathioprin* or azathropsin or azatioprina or azatox or azatrilem or azopi or azoran or azothioprin* or azothioprine or am94r510ms or bw 57 322 or bw 57322 or bw57-322 or bw57322 or colinsan or immuran or immurel or immuthera or imunen or imuprin or Imuran* or imurek or imurel or imuren or jayempi or mrk240iy2l or nsc 39084 or nsc39084 or oraprine or ozathuia or Thioazeprine or thioprine or transimune or zytrim).ti,ab,kw,kf,rn.
35. Methotrexate/ use medall,cctr
36. methotrexate derivative/ or methotrexate/ use oemezd
37. (Methotrexate or abitrexate or adx 2191 or adx2191 or amethopterin or amethopterine or ametopterine or antifolan or biotrexate or brimexate or canceren or cl 14377 or cl14377 or emt 25299 or emt25299 or emtexate or emthexat* or emtrexate or enthexate or farmitrexat* or farmotrex or folex or ifamet or imeth or jylamvo or lantarel or ledertrexate or lumexon or maxtrex or metatrexan or metex or methoblastin or methohexate or methotrate or methotrexate* or methylaminopterin* or metical or metoject or metothrexat* or metotrexat* or metotrexin or metrex or metrotex or mexate or mpi 2505 or mpi 5004 or mpi2505 or mpi5004 or MTX or neotrexate or nordimet or novatrex or nsc 740 or nsc740 or otrexup or r 9985 or r9985 or rasuvo or reditrex or reumatrex or texate or texorate or tremetex or trexall or trexeron or wr 19039 or wr19039 or xaken xatmep or zexate or zlatal).ti,ab,kw,kf,rn.
38. (biologics or biologicals or ((biological or biologic) and (agent* or product* or drug*))).ti.
39. small moledul*.ti.
40. (immunomodulator* or ((immunomodulating or immunotherapeutic) and (agent* or drug* or product*))).ti.
41. or/6-40 [interventions of interest]
42. 5 and 41 [CD and interventions]
43. limit 42 to yr="2020 -Current" [CD and drugs after 2020]

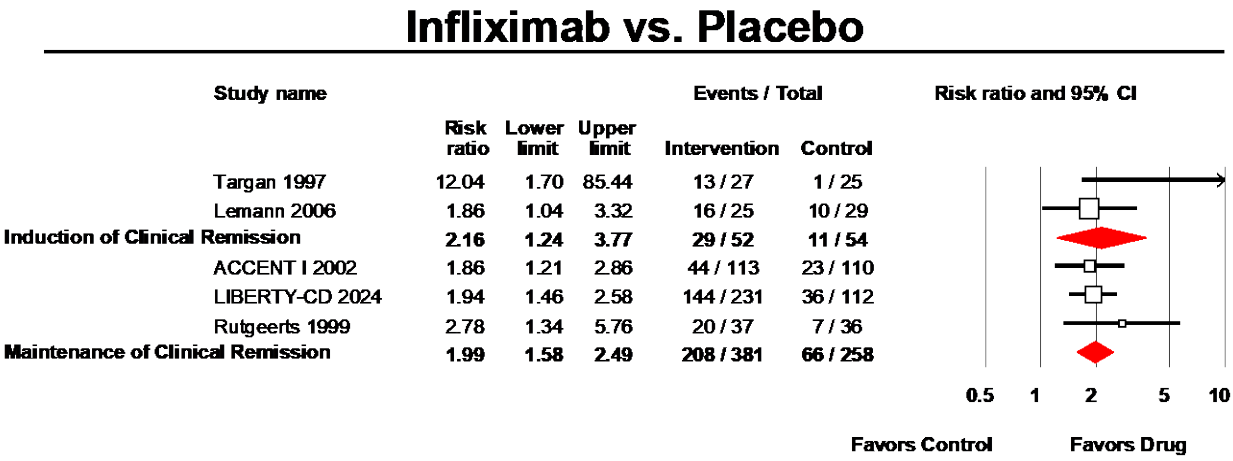
44. exp randomized controlled trial/ or controlled clinical trial.pt. or clinical trials as topic/ or (random* or placebo).ab. or trial.ti.
45. (exp animals/ not humans/) use medall
46. 44 not 45 use medall [MEDLINE RCT filter]
47. 43 and 46 use medall [RCTs in MEDLINE]
48. Randomized controlled trial/ or Controlled clinical study/ or randomization/ or intermethod comparison/ or double blind procedure/ or human experiment/ or (random$ or placebo or (open adj label) or ((double or single or doubly or singly) adj (blind or blinded or blindly)) or parallel group$1 or crossover or cross over or ((assign$ or match or matched or allocation) adj5 (alternate or group$1 or intervention$1 or patient$1 or subject$1 or participant$1)) or assigned or allocated or (controlled adj7 (study or design or trial)) or volunteer or volunteers).ti,ab. or (compare or compared or comparison or trial).ti. or ((evaluated or evaluate or evaluating or assessed or assess) and (compare or compared or comparing or comparison)).ab.
49. (random$ adj sampl$ adj7 ("cross section$" or questionnaire$1 or survey$ or database$1)).ti,ab. not (comparative study/ or controlled study/ or randomi?ed controlled.ti,ab. or randomly assigned.ti,ab.)
50. Cross-sectional study/ not (exp randomized controlled trial/ or controlled clinical study/ or controlled study/ or randomi?ed controlled.ti,ab. or control group$1.ti,ab.)
51. (((case adj control$) and random$) not randomi?ed controlled).ti,ab.
52. Systematic review.ti,ab. not (trial or study).ti.
53. (nonrandom$ not random$).ti,ab.
54. "random field$".ti,ab.
55. (random cluster adj3 sampl$).ti,ab.
56. (review.ab. and review.pt.) not trial.ti.
57. "we searched".ab. and (review.ti. or review.pt.)
58. "update review".ab.
59. (databases adj4 searched).ab.
60. (rat or rats or mouse or mice or swine or porcine or murine or sheep or lambs or pigs or piglets or rabbit or rabbits or cat or cats or dog or dogs or cattle or bovine or monkey or monkeys or trout or marmoset$1).ti. and animal experiment/
61. Animal experiment/ not (human experiment/ or human/)
62. or/49-61
63. 48 not 62 use oemezd [Embase RCTs filler]
64. 43 and 63 use oemezd [Embase RCTs]
65. limit 47 to dt=20200701-20240814 use medall [Limit not valid in CCTR,Embase; records were retained]
66. limit 47 to ed=20200701-20240814 use medall [Limit not valid in CCTR,Embase; records were retained]
67. limit 64 to dd=20200701-20240814 use oemezd [Limit not valid in CCTR,Ovid MEDLINE(R); records were retained]
68. limit 64 to dc=20200701-20240814 use oemezd [Limit not valid in CCTR; records were retained]
69. 47 and (2021* or 2022* or 2023* or 2024*).ep.
70. 43 use cctr
71. or/65-70 [CD interventions from July 2020 three databases]
72. limit 71 to english language
73. (child/ or Pediatrics/ or Adolescent/ or Infant/ or adolescence/ or newborn/) not (adult/ or aged/)
74. 72 not 73

75. (baby or babies or child or children or pediatric* or paediatric* or peadiatric* or infant* or infancy or neonat* or newborn* or new born* or adolescen* or preschool or pre-school or toddler*).ti. not (adult* or elder* or senior* or men or women).tw.
76. 74 not 75
77. remove duplicates from 75

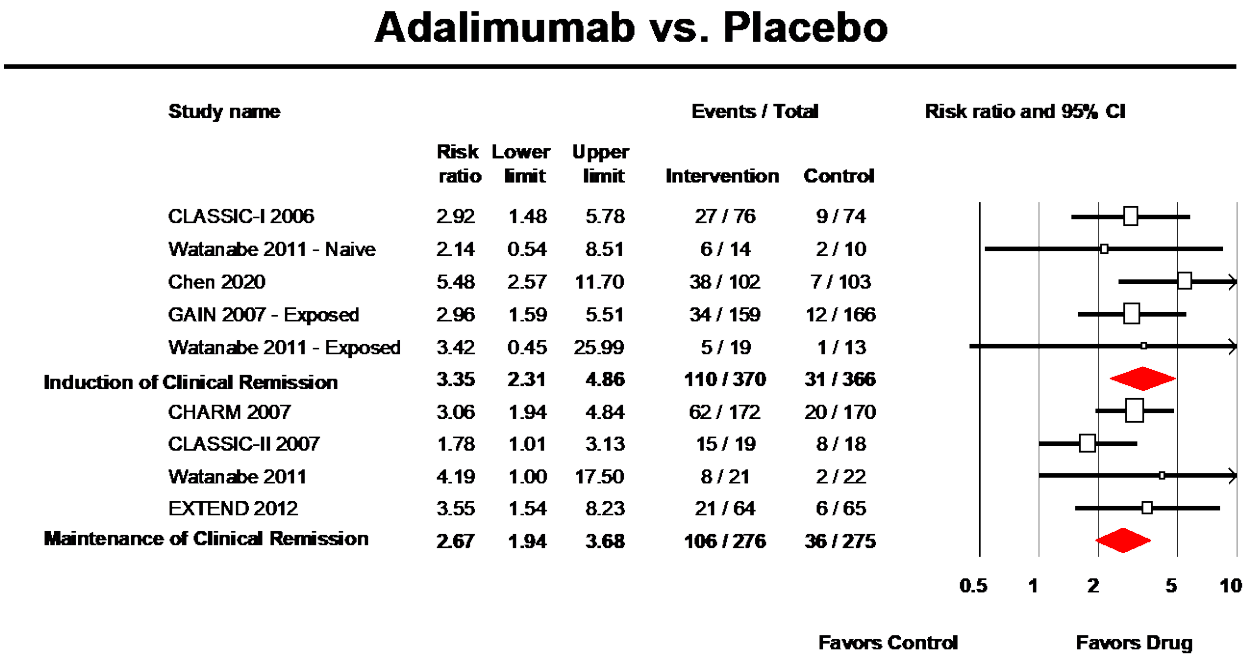
eTable 3: Interpretation of the Certainty in Evidence of Effects Using the Grading of Recommendations Assessment, Development and Evaluation Framework

Certainty	Description
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very Low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

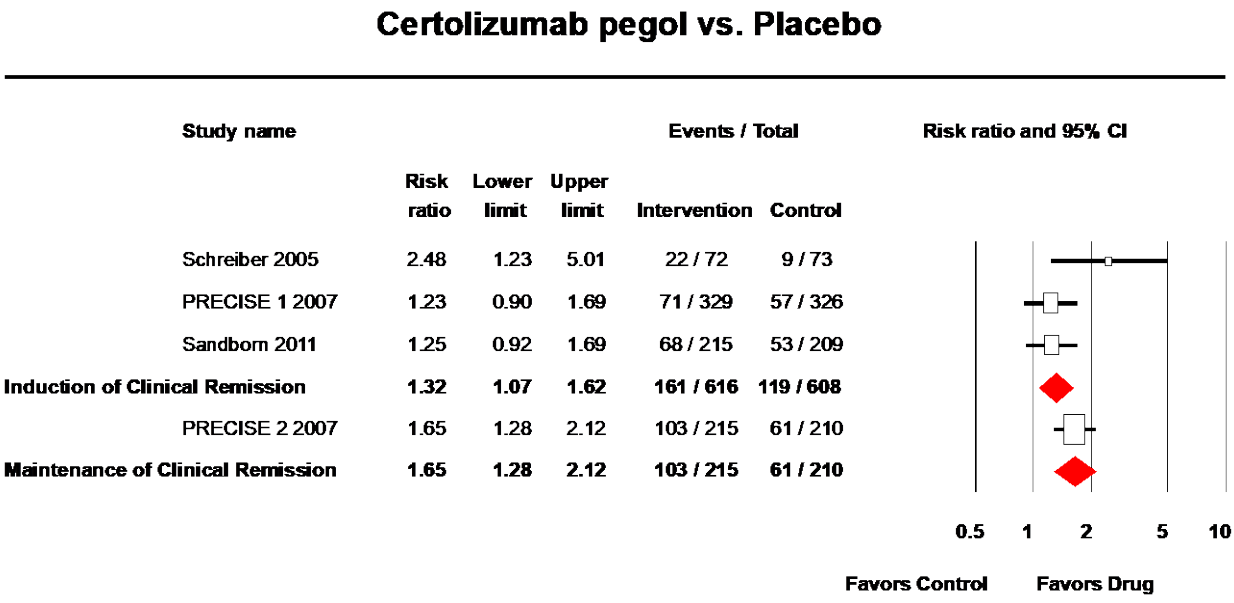
eFigure 1: Forest plot summarizing efficacy of INFLIXIMAB for induction and maintenance of remission in patients with moderately to severely active CD



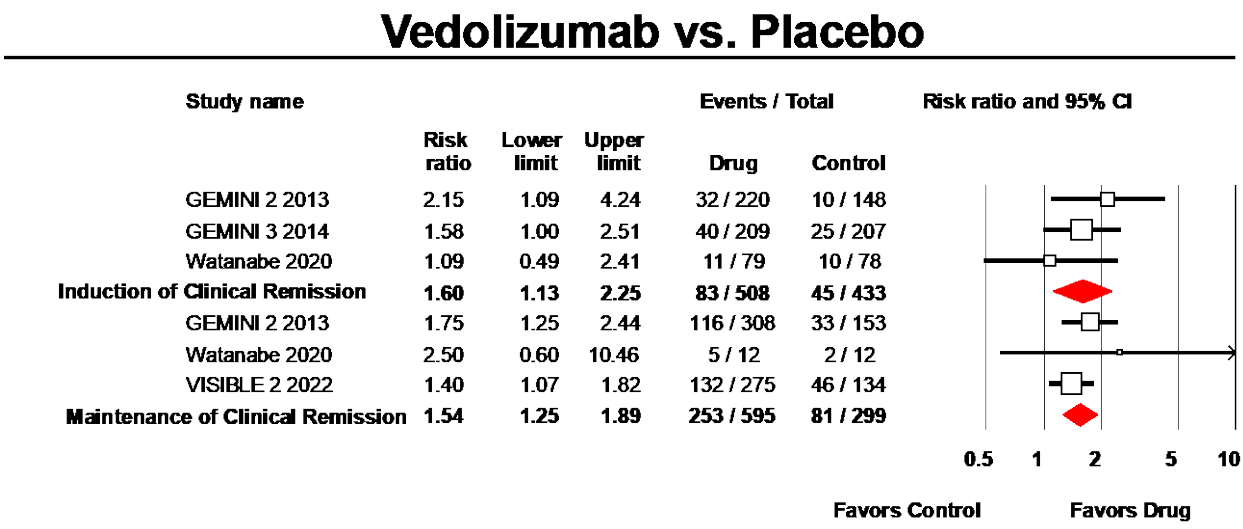
eFigure 2: Forest plot summarizing efficacy of ADALIMUMAB for induction and maintenance of remission in patients with moderately to severely active CD



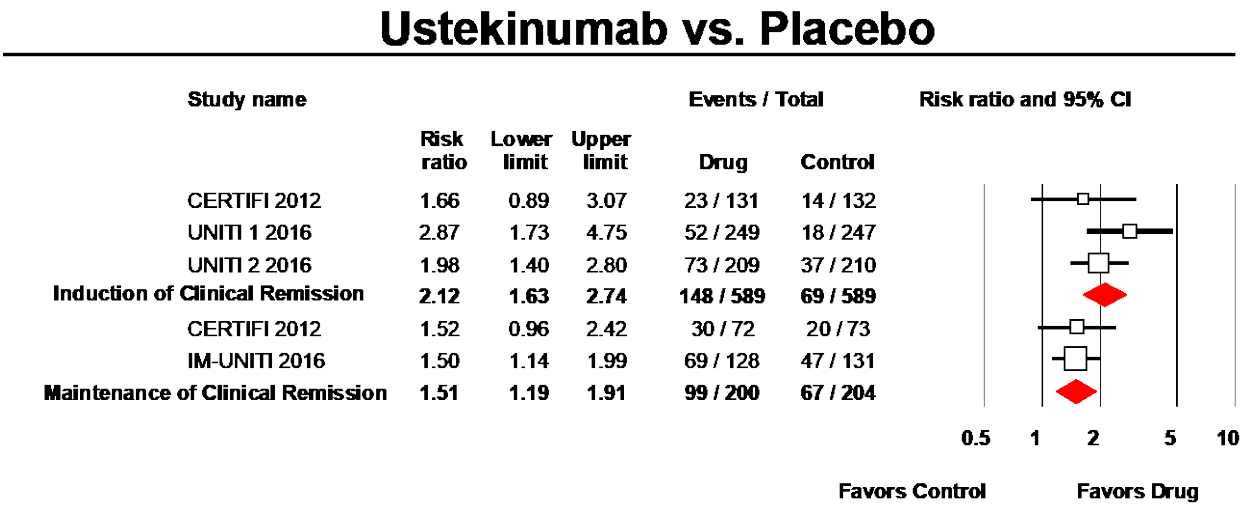
eFigure 3: Forest plot summarizing efficacy of CERTOLIZUMAB PEGOL for induction and maintenance of remission in patients with moderately to severely active CD



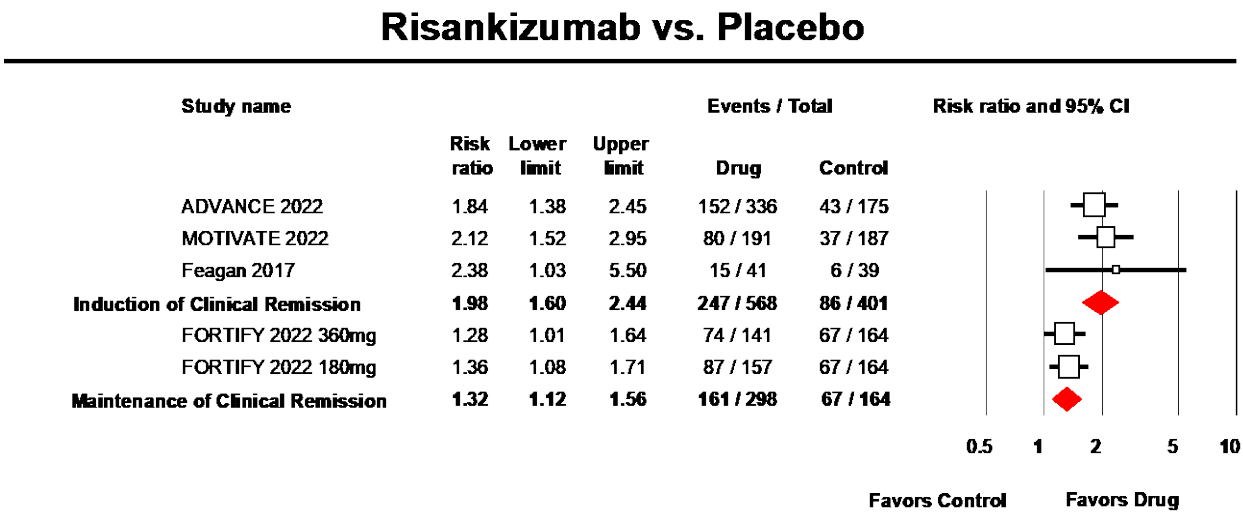
eFigure 4: Forest plot summarizing efficacy of VEDOLIZUMAB for induction and maintenance of remission in patients with moderately to severely active CD



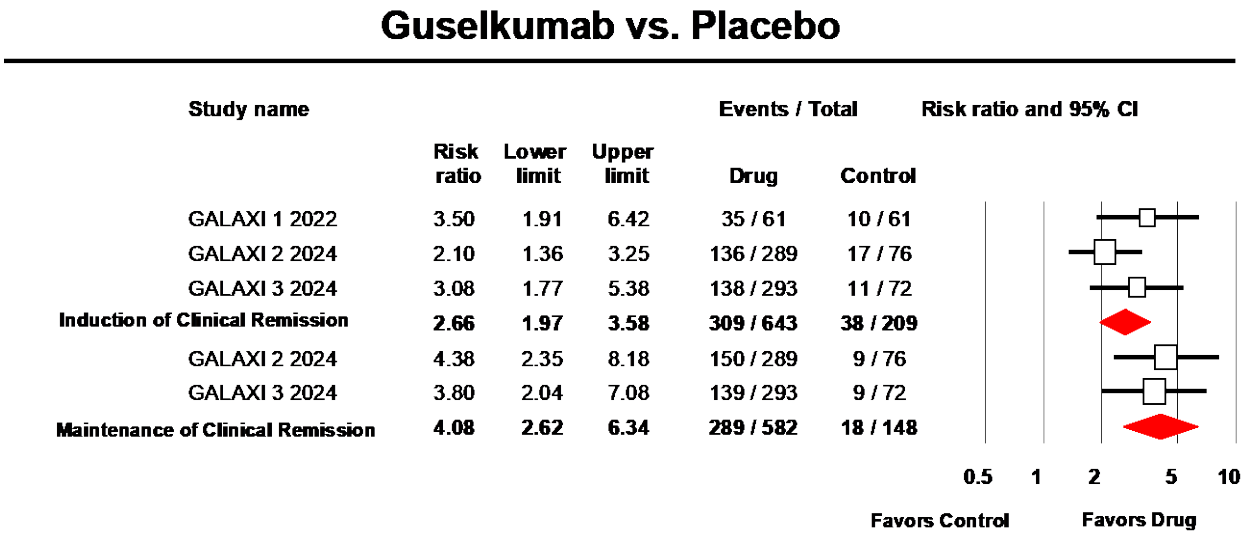
eFigure 5: Forest plot summarizing efficacy of USTEKINUMAB for induction and maintenance of remission in patients with moderately to severely active CD



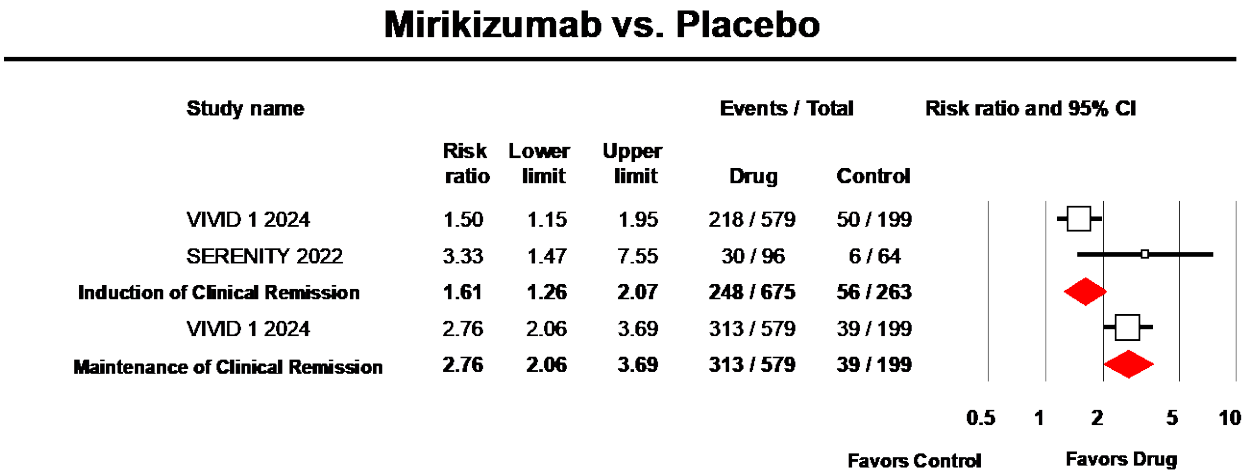
eFigure 6: Forest plot summarizing efficacy of RISANKIZUMAB for induction and maintenance of remission in patients with moderately to severely active CD



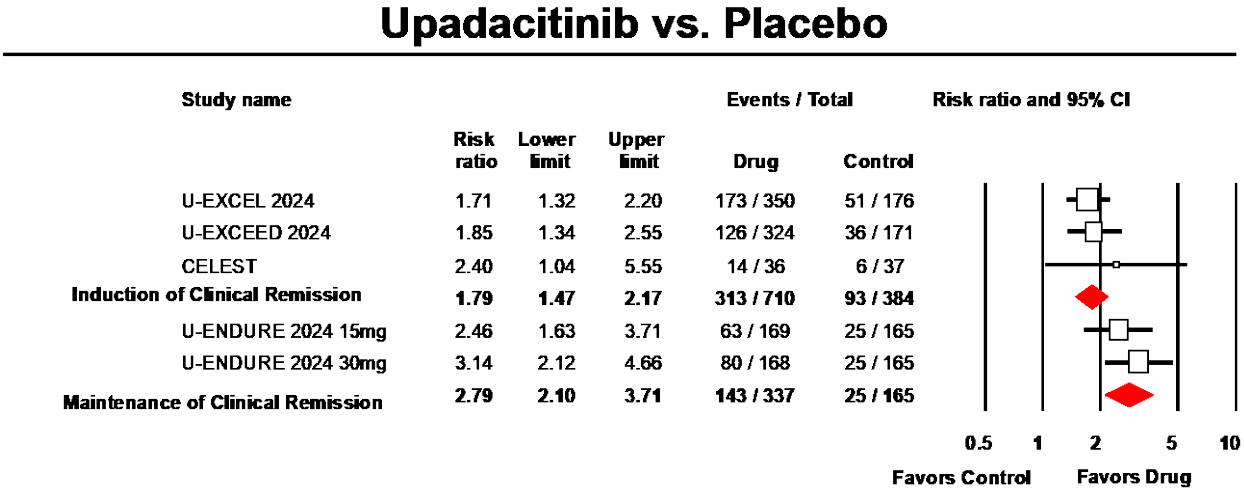
eFigure 7: Forest plot summarizing efficacy of GUSELKUMAB for induction and maintenance of remission in patients with moderately to severely active CD



eFigure 8: Forest plot summarizing efficacy of MIRIKIZUMAB for induction and maintenance of remission in patients with moderately to severely active CD

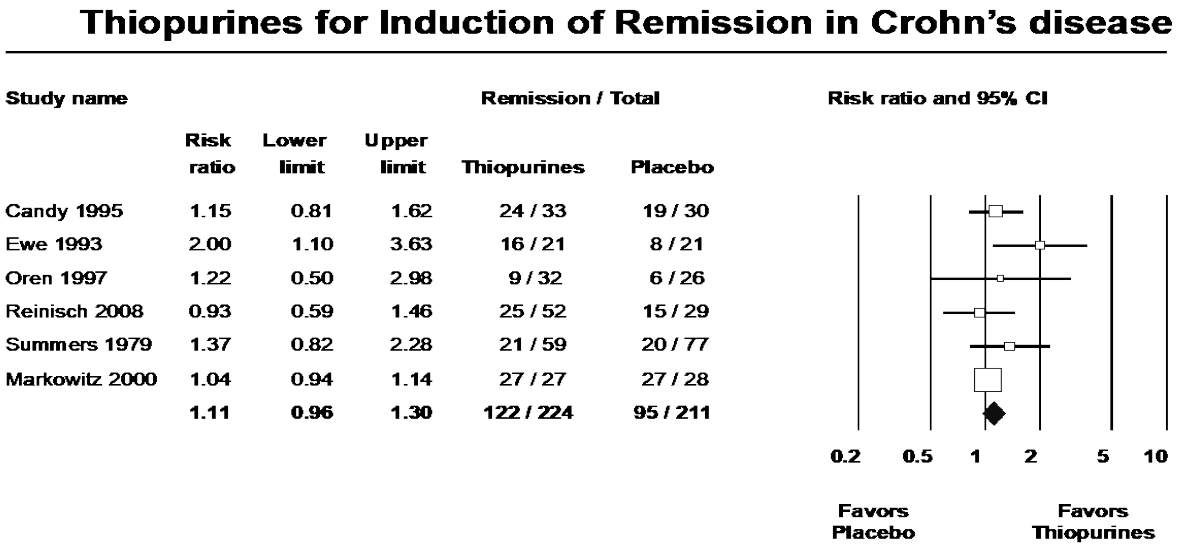


eFigure 9: Forest plot summarizing efficacy of UPADACITINIB for induction and maintenance of remission in patients with moderately to severely active CD

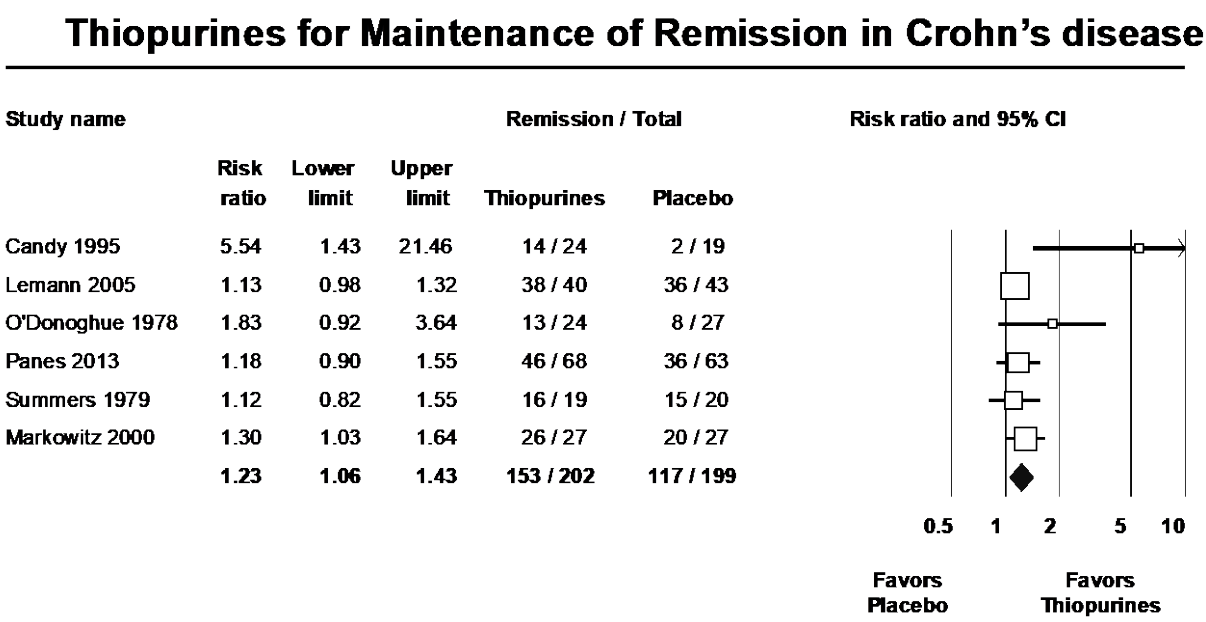


eFigure 10: Forest plot summarizing efficacy of THIOPURINES for (A) induction and (B) maintenance of remission in patients with moderately to severely active CD

A

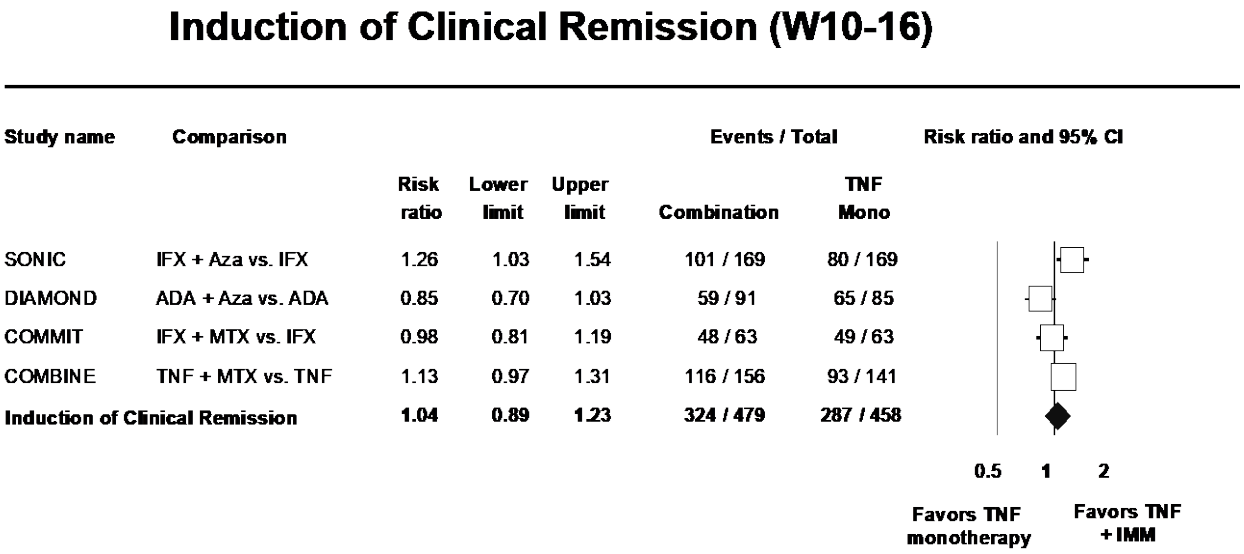


B

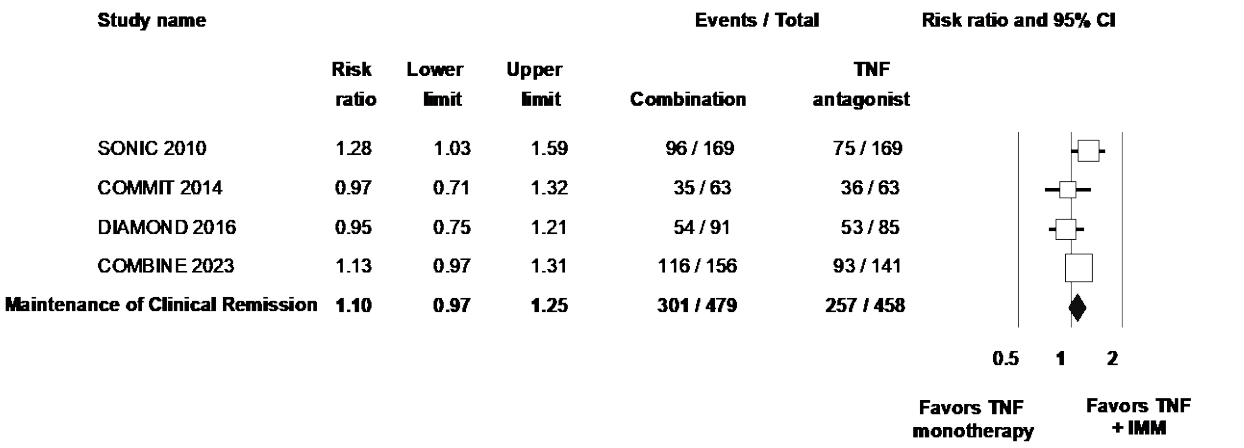


eFigure 11: Forest plot summarizing efficacy of combined TNF antagonist and immunomodulator versus TNF antagonist monotherapy for (A) induction and (B) maintenance of remission

A

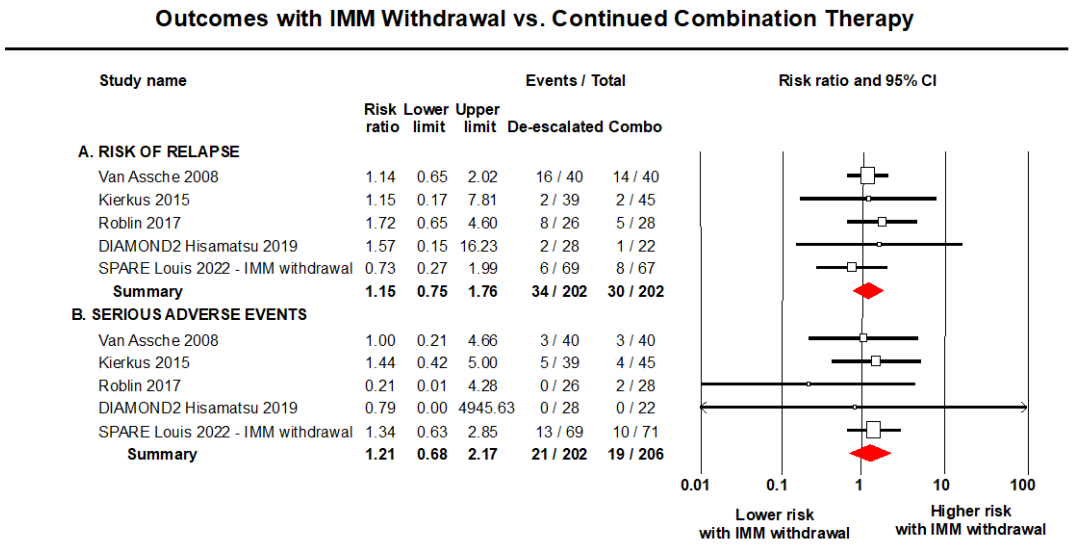


B

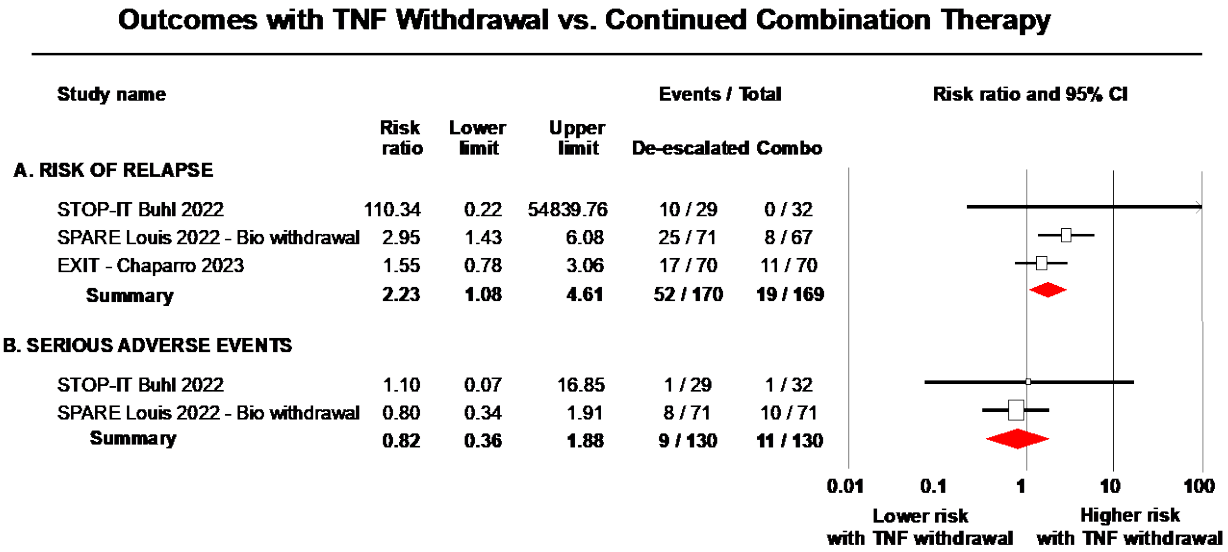


eFigure 12: Forest plot summarizing (A) efficacy and safety of stopping immunomodulator (and continuing biologic monotherapy) vs. continuing combination therapy AND (B) efficacy and safety of stopping TNF antagonist (and continuing immunomodulator monotherapy) vs continuing combination therapy in patients with moderately to severely active Crohn's disease in steroid-free remission on combination therapy

A

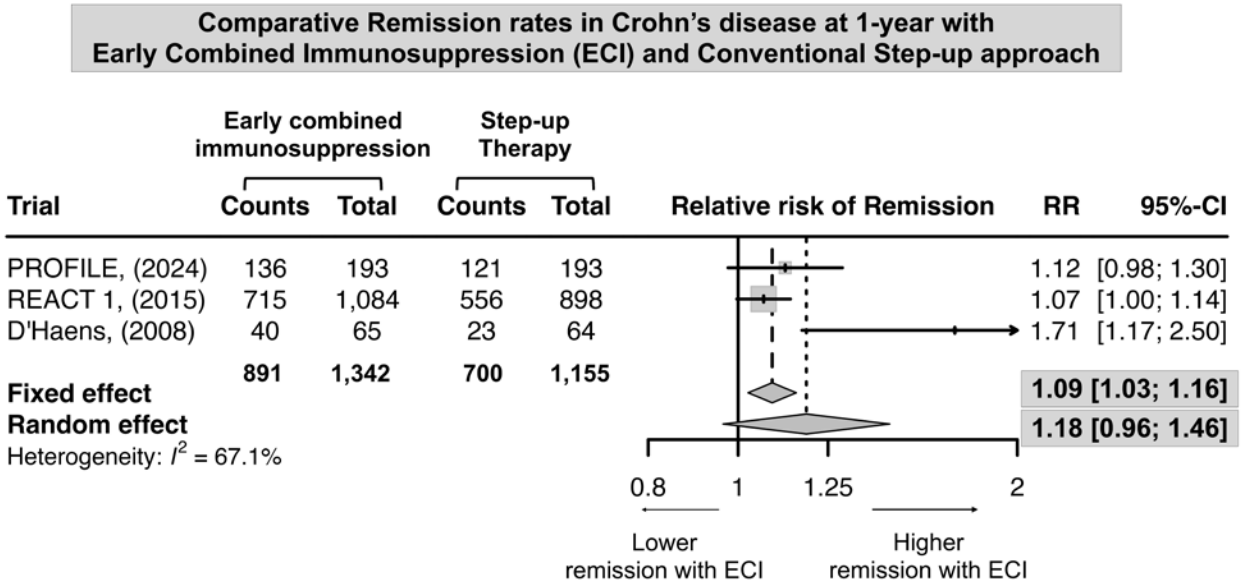


B



eFigure 13: Forest plot summarizing (A) comparative remission rates and (B) comparative disease complication rates at 1 year for early combined immunosuppression compared to conventional step up therapy efficacy in patients with moderately to severely active Crohn's disease in steroid-free remission on combination therapy

A



B