Appendix E. Additional details of the network meta-analysis

E.1 Methods of the network meta-analysis

We first define the Bayesian network meta-analysis (NMA) statistical models used to synthesize transformed outcomes, on the log hazard scale, from each randomized controlled trial (RCT). The link functions to connect these models to the different data summaries are then presented. The same statistical models are used for crisis, hospitalization days, adverse events, and serious adverse events but the link functions vary depending on what data is reported by each RCT (see main text for outcomes analyzed). The NMA models are in line with the recommendations of the National Institute for Health and Care Excellence (NICE) Decision Support Unit (DSU) technical support documents (TSD), in particular NICE DSU TSD 2. OpenBUGS code is provided for each outcome in appendix **B.4.**

For all random parameters (i.e. $\mu_{..}$ and $d_{..}$) vague $Normal(0, 0.001)$ priors were used.

Fixed-effects network meta-analysis model

When the available evidence consists of a network of multiple pairwise comparisons (i.e. AB-trials, AC-trials, BC-trials, etc.) the standard fixed effects model for NMA can be specified as follows:

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + d_{bk} = \mu_{jb} + d_{Ak} - d_{Ab} & \text{if } k \succ b \end{cases} \qquad (3)$$
$$d_{AA} = 0$$

There are *k* treatments labelled as A, B, C, etc., and treatment A is taken to be the reference treatment for the analysis. μ_{jb} is the (transformed) outcome in study *j* on 'baseline' treatment *b* which will vary across studies. d_{bk} is the fixed effect of treatment *k* relative to 'baseline treatment' *b*. d_{bk} are identified by expressing 0them in terms of the reference treatment A: $d_{bk} = d_{Ak} - d_{Ab}$ with $d_{AA} = 0$.

Random-effects network meta-analysis model

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \succ b \end{cases} \qquad (4)$$

$$\delta_{jbk} \sim Normal(d_{bk}, \sigma^2) = Normal(d_{Ak} - d_{Ab}, \sigma^2)$$
$$d_{AA} = 0$$

δ_{jbk} is the trial-specific treatment effect of *k* relative to treatment *b*. These trial-specific effects are drawn from a random-effects distribution: $\delta_{jbk} \sim N(d_{bk}, \sigma^2)$. Again, the pooled effects, d_{bk}, are identified by expressing them in terms of the reference treatment A. The heterogeneity σ^2 is assumed constant for all treatment comparisons. (A fixed effect model is obtained if σ^2 equals zero.)

This random-effects model treats multiple-arm trials (>2 treatments) without taking account of the correlations between the trial-specific δs that they estimate. Bayesian random-effects models with a heterogeneity parameter for d_{Ak} can be easily extended to fit trials with 3 or more treatment arms by decomposing a multivariate normal distribution as a series of conditional univariate distributions.[1]

$$\begin{pmatrix} \delta_{jbk_1} \\ \vdots \\ \delta_{jbk_p} \end{pmatrix} \sim Normal\left(\begin{pmatrix} d_{bk_1} \\ \vdots \\ d_{bk_p} \end{pmatrix}, \begin{pmatrix} \sigma^2 & \cdots & \frac{\sigma^2}{2} \\ \vdots & \ddots & \vdots \\ \frac{\sigma^2}{2} & \cdots & \sigma^2 \end{pmatrix} \right) \quad (5)$$

Then the conditional univariate distributions for arm *i* given the previous *1,….(i-1)* arms are:

$$\delta_{jbk_i} | \begin{pmatrix} \delta_{jbk_1} \\ \vdots \\ \delta_{jbk_{i-1}} \end{pmatrix} \sim Normal\left(d_{bk_i} + \frac{1}{i}\sum_{j=1}^{i-1} \left(\delta_{jbk_j} - d_{bk_j} \right), \frac{(i-1)}{2i}\sigma^2 \right) \quad (6)$$

Random-effects network meta-analysis model with constant covariate interaction term

$$\theta_{jk} = \begin{cases} \mu_{jb} & \text{if } k = b \\ \mu_{jb} + \delta_{jbk} & \text{if } k \succ b \end{cases}$$

$$\delta_{jbk} = \begin{cases} Normal\left(d_{Ak} - d_{Ab} + \beta X_j, \sigma^2\right) & \text{if } b = A \\ Normal(d_{Ak} - d_{Ab}, \sigma^2) & \text{if } b \neq A \end{cases}$$

$$d_{AA} = 0$$

X_j is the trial-specific covariate value. β is the corresponding treatment-by-covariate interaction term, which is the same for all interventions.

Link functions for shared parameter models

As described above, the available data is connected to the model via the likelihood and the link function $\theta_{jk} = g(\gamma_{jk})$. If different data summaries are used by different studies, it is necessary to use a shared parameter model, where different link functions and likelihoods are used for each study[2]. Our underlying model will be on the log hazard ratios $d_{..}$, which can be fixed or random and include meta-regression effects as discussed. In SCD it will be necessary to connect the following data summaries.

1) Estimated annualized event log rate $\log(\lambda_{jk})$ (mean or median) with standard error se_{jk} are modelled with identity link and Normal likelihood

$$\log(\lambda_{jk}) \sim Normal(\theta_{jk}, se_{jk}^2)$$

2) Total number of events r_{jk} over exposure E_{jk} are modelled with log link and Poisson likelihood

$$r_{jk} \sim Pois(\lambda_{jk} E_{jk})$$

$$\theta_{jk} = \log(\lambda_{jk})$$

3) Mean number of events per patient $\bar{r}_{jk}$ over n_{jk} patients is transformed to total number of events r_{jk} and modelled as type 2 data.
4) Number of patients w_{ij} with ≥1 event over mean follow-up time t_{ij} are modelled with a binomial likelihood and complementary log log (cloglog) link with log time as offset

$$r_{jk} \sim Binomial(P_{jk}, n_{jk})$$
$$cloglog(P_{jk}) = \log(-\log(P_{jk})) = \log(t_{jk}) + \theta_{jk}$$

5) Log hazard ratio or log rate ratio $\log(hr_{jk})$ with standard error se_{jk} between active arm k and control arm b. This is slightly different as we no longer have data on both arms, only on the contrasts.

$$\log(hr_{jk}) \sim Normal(\theta_{jk}, se_{jk}^2), \text{ for } k \succ b$$

and

$$\theta_{jk} = d_{bk} \text{ if fixed effects}$$
$$\theta_{jk} = \delta_{jbk}, \text{ if random effects or meta-regressions}$$

An adjusted standard error is needed for log hazard ratios if trials have more than 2 arms, as there is induced correlation between arms due to the common control.

Table 1 Summary of analyses planned for different outcome measures on each of the outcomes

Outcome	Outcome measure	Analysis planned	Why this analysis
Crisis	Total pain crises	Poisson likelihood, log link (Type 2 data)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.

	Mean or rate pain crises	Scale to total pain crises	Mean per patient gives total when scaled by patient number.
	Patients with ≥1 pain crisis	Binomial likelihood with cloglog link (type 4 data)	At most one such 'event' per patient, giving a binomial. Convert to log hazard scale modelled via Poisson using a cloglog function and a log follow-up time offset.
	Risk ratio/hazard ratio of crisis	Normal likelihood with identity link (type 5 data)	Direct observation of difference in log rates/hazards.
Hospitalization	Total hospitalization days	Poisson likelihood, log link (Type 2)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.
	Mean, median, or rate hospitalization days	Scale to total hospitalization days	Mean per patient gives total when scaled by patient number.
Adverse events or serious adverse events	Total events	Poisson likelihood, log link (Type 2)	Multiple events per patient so modelling underlying log hazard with a Poison likelihood.
	No. of patients with ≥ 1 event	Binomial likelihood with cloglog link (type 4 data)	At most one such 'event' per patient, giving a binomial. Convert to log hazard scale modelled via Poisson using a cloglog function and a log follow-up time offset.
	% patients with ≥ 1 event	Scale to number of patients with ≥ 1 event	Percentage gives total when multiplied by patient numbers

E.2 Outcome definitions used in the analyzed trials

Table 2: Definitions of VOC used in 5 RCTs included in base case crisis network

Study	Treatments	Crisis
Ataga 2017	Placebo, High-dose Crizanlizumab, Low-dose Crizanlizumab	Sickle cell–related pain crises were defined as acute episodes of pain, with no medically determined cause other than a vaso-occlusive event, that resulted in a medical facility visit and treatment. with oral or parenteral narcotic agents or with a parenteral nonsteroidal anti-inflammatory drug. The acute chest syndrome, hepatic sequestration, splenic sequestration, and priapism were also considered to be crisis events.
Ataga 2011	Placebo, senicapoc	A painful crisis was defined as an episode of acute pain with no cause other than a vaso-occlusive event that required a medical facility visit and treatment with oral or parenteral narcotics, or parenteral non-steroidal anti-inflammatory drugs. Included in the definition of painful crisis were acute chest syndrome, hepatic sequestration, splenic sequestration, priapism, stroke and death (with the exception of homicide, suicide, or accidental death). To ensure consistency across sites, all protocol-defined sickle-related painful crises identified by the Investigators that resulted in a visit to a medical facility were adjudicated by an independent, blinded, Crisis Review Committee (CRC).
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	An independent, blinded crisis review committee adjudicated all sickle cell painful crises and related adverse event data (Document S1). A painful crisis was defined as a period of severe pain (with no explanation other than SCD) lasting 4 or more hours in duration, requiring a visit to a health care facility, and requiring parenteral opiate or other narcotic for relief
Pace 2003	Placebo, NAC (low-dose) 600 mg/day, NAC (mid-dose) 1200mg/day, NAC (high-dose) 2400mg/day	Defined as a visit to a medical facility that lasted more than 4 hr for acute pain related to vaso-occlusion requiring parenteral narcotics. The occurrence of acute chest syndrome, priapism, splenic, or hepatic sequestration was also counted as a VOC episode. Acute chest syndrome included those subjects with chest wall pain and a new infiltrate on chest X ray.
Niihara 2018	Placebo, L-glutamine	A pain crisis was defined as pain leading to treatment with a parenterally administered narcotic or ketorolac in an emergency department (ED) (or outpatient treatment center) or during hospitalization.

Table 3: Adverse events reported in the 8 RCTs in the base case adverse events network

Study	Treatments	Outcome name	Adverse events included
Ataga 2017	Placebo, High-dose Crizanlizumab,	Adverse events	"Headache, Back pain, Nausea, Arthralgia, Pain in extremity, Urinary tract infection, Upper respiratory tract infection, Pyrexia, Diarrhea,

	Low-dose Crizanlizumab		Musculoskeletal pain, Pruritus, Vomiting, Chest pain
		Serious adverse events	Pyrexia, Influenza, Pneumonia
Ataga 2011	Placebo, senicapoc	Adverse events	Nausea, Urinary tract Infection, Headache, Arthralgia, Upper respiratory tract Infection, Vomiting, Pyrexia, Pneumonia, Back pain, Pain in extremity, Nasopharyngitis, Cough, Constipation, Fatigue, Hypokalaaemia, Haematuria, Diarrhoea, Abdominal pain, Pharyngolaryngeal pain, Pruritus, Drug hypersensitivity
Ataga 2008	Placebo, senicapoc (low-dose), senicapoc (high-dose)	Adverse events	Diarrhea, Nausea, Constipation, Gastroenteritis, Upper respiratory tract infection, Chest pain, Increased SGOT, Arthralgia, Back pain
Niihara 2018	Placebo, L-glutamine	Adverse events	Tachycardia, Constipation, Nausea, Vomiting, Abdominal pain upper, Diarrhea, Chest pain (noncardiac), Fatigue, Urinary tract infection, Pain in extremity, Back pain, Headache, Dizziness, Nasal congestion
		Serious adverse events	A serious adverse event was defined as any adverse event, occurring while the patient was receiving the trial medication or placebo at any dose, that resulted in death, a life-threatening event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or clinically significant disability or incapacity, or a congenital anomaly or birth defect. Notable medical events that might not have resulted in death, been life-threatening, or required hospitalization could be considered serious adverse events if it was determined, on the basis of appropriate medical judgment, that they could place the patient's health in jeopardy and might require medical or surgical intervention to prevent one of the outcomes listed in the definition of serious adverse events.

Glassberg 2017	mometasome placebo		Hoarseness of voice, thrush, sore throat
Sins 2017	NAC placebo	Adverse events	Gastro-intestinal complaints, Pruritus / Rash, plus Discontinuation of study drug or placebo because of adverse event and serious adverse events
		Serious adverse events	Acute Chest Syndrome, Liver/spleen sequestration, Pyelonefritis with admission, Cholelithiasis with admission, Gastrointestinal perforation, Pulmonary embolism, Pneumonia with admission
Wun 2013	Prasugrel, placebo	Any serious adverse event	No detail given but they were non-hemorrhagic events
NCT02482298	Placebo TICAGRELOR 10MG, TICAGRELOR 45MG	Adverse events	Sickle cell anaemia with crisis, Abdominal pain, nausea, toothache, vomiting, fatigue, non-cardiac chest pain, pain, pneumonia, Upper respiratory tract infection, Urinary tract infection, Arthralgia, Back pain, Musculoskeletal chest pain, Musculoskeletal pain, pain in extremity, Headache, Dysmenorrhoea, Cough, Epistaxis, Oropharyngeal pain
		Serious adverse events	Reticulocytopenia, Sickle cell anemia with crisis, Local swelling, Hepatic ischemia, Cellulitis, Gastroenteritis, Lower respiratory tract infection, Face injury, Arthralgia, Back pain, Musculoskeletal chest pain, headache, Acute chest syndrome, Vascular occlusion
Glassberg 2017	mometasome placebo		Hoarseness of voice, thrush, sore thr`oat

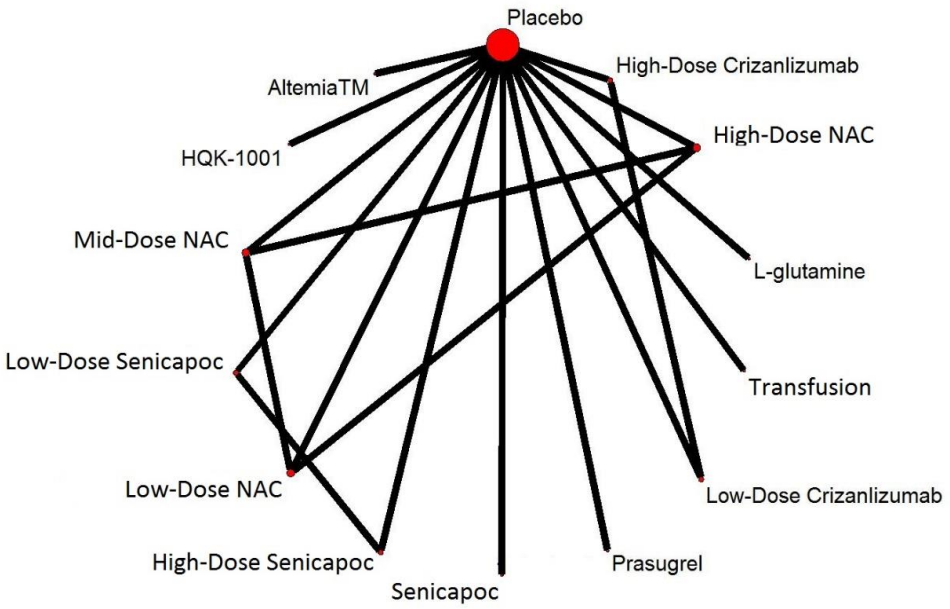
E.3 Additional results of the network meta-analysis

Extended network for potential indirect evidence

We wished to assess whether additional direct or indirect evidence would be provided on comparators studied in the 9 RCTs of the adult only NMA by including the 25 excluded non-adult RCTs as well as Vichinsky 2010 on transfusions under the assumption that their standard of care was a placebo. To do this we plotted the evidence networks including non-adult RCTs reporting on crisis, hospitalization days, adverse events, and serious adverse events and connected to high-dose crizanlizumab. However, there were only additional RCTs connected to high-dose crizanlizumab reporting on the crisis outcome. No additional RCTs connected to high-dose crizanlizumab reported on hospitalization days, adverse events, and serious adverse events.

The extended evidence network for crisis is presented in Figure 1. This network consists of 9 RCTs, including 4 RCTs not in the adult only network: Daak 2018 (AltemiaTM vs placebo)[3], Heeney 2016 (prasugrel vs placebo)[4], Reid 2014 (HQK-1001 vs placebo)[5], Vichinsky 2010 (transfusions vs standard of care)[6]. The extended network included 3 treatments not in the base case (AltemiaTM, HQK-1001, and Prasugrel). However, these additional RCTs did not provide direct or indirect evidence on any comparisons in the base case network.

Figure 1. Network of evidence for crisis in the extended population. Consists of 9 RCTs and 14 treatments.*

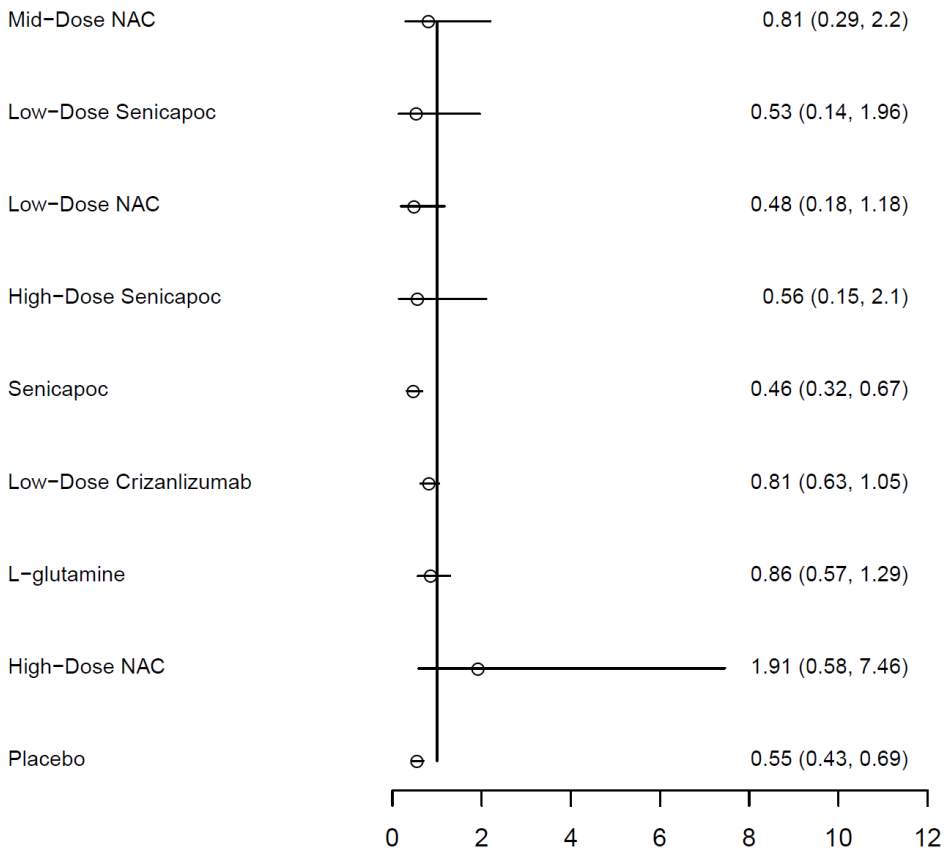


* Network included adult (base case) and non-adult studies. Adult studies: Ataga 2017 (crizanlizumab vs placebo), Ataga 2011 (senicapoc vs placebo), Ataga 2008 (senicapoc low-dose, senicapoc high-dose vs placebo), Pace 2003 (NAC vs placebo), Niihara 2017 (L-glutamine vs placebo), Vichinsky 2010 (transfusion vs placebo). Non-adult studies: Daak 2018 (AltemiaTM vs placebo), Heeney 2016 (prasugrel vs placebo), Reid 2014 (HQK-1001 vs placebo)

Sensitivity analysis using >18 years old subgroup results from Niihara 2018 on L-glutamine

As our target population was patients ≥16 years old the Niihara 2018 study with 51 patients aged 5-12, 67 aged 13-18, and 112 aged >18 potentially differed in important effect modifiers. We used the reported rate ratio of 0.64 with 95% confidence interval (0.45, 0.89) in a subgroup of patients aged >18 years old to repeat our NMA. The results are presented as forest plots in Figure 2 with p-value table in Table 4 and pairwise results in Table 13. Notably, the hazard ratio for crises on crizanlizumab vs L-glutamine is 0.86 (0.57, 1.29) with p-value 0.77; this is higher and more uncertain that the hazard ratio of 0.67 (0.51, 0.88) and p-value >0.99 estimated using the full results of Niihara 2018.

Figure 2. Forest plot using >18 years old subgroup results from Niihara 2018 on L-glutamine



Sd

Table 4. Bayesian probabilities that crizanlizumab is superior or inferior on each outcome analyzed using >18 year old subgroup results from Niihara 2018.

Treatment	Probability superior
Placebo	>0.9999
NAC (high-dose 2400mg)	0.1495
L-glutamine	0.7707
Low-Dose Crizanlizumab	0.9454
Senicapoc	>0.9999
High-Dose Senicapoc	0.8066
Low-Dose NAC	0.9429
Low-Dose Senicapoc	0.8354
Mid-Dose NAC	0.6649

Model assessment of the crisis network meta-analysis

Model fit and meta-regressions were explored. The base case fixed effects model fit well (total residual deviance close to number of data points[7]) but the meta-regressions did not converge (Gelman-Rubin Rhat statistic far from 1.000, very wide credible intervals for the regression coefficient). This was because there was only one RCT on each treatment contrast. Deviance and DIC do not in any case suggest evidence of effect modification as they are similar to the fixed effects analysis.

Table 5. Crisis among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	14	15.44 (6.11, 25.85)	102.8	NA	NA
Proportion female FE	14	15.59 (6.14, 26.23)	102.9	45.66 (-83.88, 188.64)	1.681

Mean age FE	14	16.07 (6.23, 27.08)	103.8	-3.89 (-4.95, -2.85)	9.652
Proportion HbSS FE	14	15.4 (6.15, 25.73)	102.7	44.14 (8.16, 72.78)	2.018
Proportion HU use FE	14	15.29 (6.18, 25.44)	102.5	76.07 (47.4, 106.76)	7.392
Trial duration FE	14	15.18 (6, 25.34)	102.5	-7.35 (-50.24, 37.51)	7.528
Proportion black FE	14	15.77 (6.37, 26.29)	103.3	-2.93 (-78.26, 72.71)	21.211

Model assessment of the hospitalization days network meta-analysis

Model assessment and exploration of meta-regressions are presented in Table 6. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 6. Hospitalization days among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	9	10.32 (3.02, 18.67)	72.69	NA	NA
Proportion female FE	9	10.46 (2.93, 19.2)	72.6	37.75 (-98.37, 172.76)	24.655
Mean age FE	9	10.52 (3.09, 19.2)	72.57	-5.85 (-7.09, -4.67)	6.029
Proportion HbSS FE	9	10.28 (2.91, 18.68)	72.71	39.4 (-33.02, 108.38)	21.868

Proprotion HU use FE	9	10.22 (2.99, 18.53)	72.44	78.51 (15.98, 139.67)	7.582
Trial duration FE	9	10.03 (2.9, 18.16)	72.33	16.54 (-3.57, 36.27)	34.345
Proportion black FE	9	9.99 (3.05, 17.91)	72.25	29.18 (-26.53, 86)	27.376

Model assessment for the adverse events network meta-anlaysis

Model assessment and exploration of meta-regressions are presented in Table 7. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 7. Adverse events among the adult population: Model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	11	12.38 (4.25, 21.55)	71.72	NA	NA
Proportion female FE	11	12.51 (4.27, 21.81)	71.96	57.94 (2, 114.04)	1.838
Mean age FE	11	12.35 (4.11, 21.73)	71.46	0.27 (-4.32, 4.95)	38.731
Proportion HbSS FE	11	12.65 (4.22, 22.29)	71.84	-45.33 (-137.28, 42.08)	10.813
Proprotion HU use FE	11	12.15 (4.25, 21.02)	71.4	-25.25 (-81.24, 28)	5.985

Trial duration FE	11	12.02 (4.18, 20.87)	71.11	21.33 (-1.45, 43.98)	20.575
Proportion black FE	11	12.31 (4.33, 21.3)	71.61	-20.3 (-48.26, 3.68)	4.349

Model assessment for the serious adverse events network meta-anlaysis

Model assessment and exploration of meta-regressions are presented in Table 8. The base case fixed effects model fits well (total residual deviance close to number of data points). Meta-regressions did not converge (Rhat statistic far from 1.000 and very wide credible intervals on the regression coefficient) as there was only one study on each treatment contrast. The deviance and DIC do not in any case suggest evidence of effect modification.

Table 8. Serious adverse events among the adult population: model comparison

Model	Number data points	Total residual deviance	DIC	Regression coefficient	Gelman-Rubin Rhat for regression
Base FE	12	13.49 (4.86, 23.2)	70.89	NA	NA
Proportion female FE	12	13.87 (4.96, 23.98)	71.27	-57.35 (-183.99, 65.33)	1.204
Mean age FE	12	13.98 (5.08, 24.06)	71.49	-2.06 (-4.45, 0.36)	40.773
Proportion HbSS FE	12	14.08 (5.04, 24.24)	71.96	51.6 (35.74, 65.75)	1.652
Proportion HU use FE	12	13.49 (4.92, 23.1)	70.99	-140.71 (-210.66, -68.54)	13.326
Trial duration FE	12	13.62 (4.92, 23.54)	70.87	-19.04 (-34.58, -3.28)	15.267

Proportion black FE	12	13.37 (4.75, 23.13)	70.66	-5.77 (-118.35, 104.8)	36.318

B.3 OpenBUGS code for the network meta-analysis

The code for the four shared parameter models used to analyze crisis, hospitalization days, adverse events, and serious adverse events are presented below. This code was run in OpenBUGS version 3.2.3 [8] with two MCMC chains of 400,000 iterations for burn-in and 30,000 iterations for posterior sampling.

Fixed effects model used for analyzing crisis.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na2[i]) {            # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
totresdev<-totresdev2+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0      # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(E2= structure(.Data= c(6.50000E+01, 6.70000E+01, 6.60000E+01, NA, 1.44000E+02,
1.45000E+02, NA, NA, 6.92308E+00, 7.15385E+00, 6.69231E+00, NA, 1.75000E+00,
2.91667E+00, 2.33333E+00, 2.91667E+00, 7.20000E+01, 1.40308E+02, NA, NA), .Dim=c(5, 4)),
t2= structure(.Data= c(1.00000E+00, 2.00000E+00, 5.00000E+00, NA, 1.00000E+00, 6.00000E+00,
NA, NA, 1.00000E+00, 7.00000E+00, 9.00000E+00, NA, 1.00000E+00, 3.00000E+00,
8.00000E+00, 1.00000E+01, 1.00000E+00, 4.00000E+00, NA, NA), .Dim=c(5, 4)), r2=
structure(.Data= c(1.93700E+02, 1.09210E+02, 1.32660E+02, NA, 8.90000E+01, 1.06000E+02,
```

NA, NA, 5.00000E+00, 5.00000E+00, 5.00000E+00, NA, 8.00000E+00, 4.00000E+00, 1.20000E+01, 9.00000E+00, 3.04200E+02, 4.86400E+02, NA, NA), .Dim=c(5, 4)), n4= structure(.Data= c(3.80000E+01, 3.80000E+01), .Dim=c(1, 2)), ns1=0.00000E+00, ns2=5.00000E+00, ns4=0.00000E+00, ns5=0.00000E+00, na1=0.00000E+00, na2=c(3.00000E+00, 2.00000E+00, 3.00000E+00, 4.00000E+00, 2.00000E+00), na4=c(0.00000E+00, 0.00000E+00), na5=c(0.00000E+00, 0.00000E+00), nt=1.00000E+01, x= structure(.Data= c(NA, NA, NA, NA, NA, NA, 5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.53633E-01, 2.89983E+01, 8.47751E-01, 5.64014E-01, 1.00000E+00, 9.51557E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.00000E-01, 3.54833E+01, 1.00000E+00, 5.37603E-01, 2.30769E-01, 8.14103E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 4.76190E-01, 2.05286E+01, 8.49869E-01, 5.37603E-01, 5.83333E-01, 8.14103E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.39130E-01, 2.20609E+01, 9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim=c(5, 4, 6)), mx=c(5.38790E-01, 2.52754E+01, 8.49869E-01, 5.37603E-01, 9.51465E-01, 8.14103E-01), r2.base=c(1.93700E+02, 1.22000E+02, 8.90000E+01, 5.00000E+00, 8.00000E+00, 3.04200E+02), E2.base=c(6.50000E+01, 1.27500E+02, 1.44000E+02, 6.92308E+00, 1.75000E+00, 7.20000E+01), r4.base=1.90000E+01, *time4.base=4.61538E-01, n4.base=3.80000E+01, ns2.base=6.00000E+00, ns4.base=1.00000E+00)*

 # Initial values (includes initial values for meta-regressions, which are redundant)
 # Inits 1
list(B=5.00000E-01, d=c(NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00, 1.40000E+00, 1.40000E+00, 1.40000E+00, 1.40000E+00))

 # Inits 2
list(B=1.00000E-01, d=c(NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-01))

Fixed effects model used for analyzing hospitalization days.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na2[i]) {            # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
totresdev<-totresdev2+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0       # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
```

```
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns4=0.00000E+00, E2= structure(.Data= c(6.53846E+00, 1.34615E+01,    NA,
6.50000E+01,  6.70000E+01,  6.60000E+01,  8.50000E+00,  5.00000E+00,         NA,  7.20000E+01,
1.40308E+02,       NA), .Dim=c(4, 3)), t2= structure(.Data= c(1.00000E+00, 5.00000E+00,       NA,
1.00000E+00,  2.00000E+00,  6.00000E+00,  1.00000E+00,  3.00000E+00,         NA,  1.00000E+00,
4.00000E+00,       NA), .Dim=c(4, 3)), r2= structure(.Data= c(6.95300E+01,  9.34500E+01,       NA,
4.46550E+02,  2.68000E+02,  4.53420E+02,  5.30000E+01,  9.00000E+00,         NA,  1.81000E+01,
1.21000E+01,       NA), .Dim=c(4, 3)), ns1=0.00000E+00, ns2=4.00000E+00, na1=0.00000E+00,
na2=c(2.00000E+00,    3.00000E+00,    2.00000E+00,    2.00000E+00),    nt=6.00000E+00,    x=
structure(.Data= c(  NA,    NA,    NA,    NA,    NA,    NA, 4.42308E-01, 3.19615E+01, 9.61538E-01,
5.23307E-01, 3.07692E-01, 8.09945E-01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,
NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA, 5.50505E-01, 2.80152E+01, 7.12121E-01,
6.21212E-01, 1.00000E+00, 9.19192E-01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,
NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA, 5.97015E-01, 2.88836E+01,
6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,
NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA,    NA, 5.39130E-01, 2.20609E+01,
9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01,    NA,    NA,    NA,    NA,    NA,    NA,    NA,
NA,    NA,    NA,    NA,    NA), .Dim=c(4, 4, 6)), mx=c(5.32240E-01, 2.81176E+01, 8.15057E-01,
5.23307E-01, 6.82692E-01, 8.09945E-01))


# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
list(B=5.00000E-01,  d=c(          NA,  1.00000E+00,  1.00000E+00,  1.00000E+00,  1.00000E+00,
1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00,  1.40000E+00,
1.40000E+00, 1.40000E+00))

# Inits 2
list(B=1.00000E-01, d=c(   NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01),
sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01, 7.00000E-
01))
```

Fixed effects model used for analyzing adverse events.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                    # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na2[i]) {            # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance
```

```
        # Data type 4; number of patients r4 out of n4 with >=1 event in time4
        # Binomial likelihood, cloglog link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns4){                    # LOOP THROUGH STUDIES
                mu4[i] ~ dnorm(0,.0001)          # vague priors for all trial baselines
                for (k in 1:na4[i]) {            # LOOP THROUGH ARMS
                        r4[i,k] ~ dbin(p[i,k],n4[i,k]) # Binomial likelihood
                        # model for linear predictor
                        cloglog(p[i,k]) <- log(time4[i,k]) + mu4[i] + d[t4[i,k]] - d[t4[i,1]]
                        rhat[i,k] <- p[i,k] * n4[i,k]        # expected value of the numerators
                        #Deviance contribution
                        dev4[i,k] <- 2 * (r4[i,k] * (log(r4[i,k])-log(rhat[i,k]))
                +  (n4[i,k]-r4[i,k]) * (log(n4[i,k]-r4[i,k]) - log(n4[i,k]-rhat[i,k])))        }
                        #  summed residual deviance contribution for this trial
                        resdev4[i] <- sum(dev4[i,1:na4[i]])
                }
        totresdev4 <- sum(resdev4[])           #Total Residual Deviance
totresdev<-totresdev2+totresdev4+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0      # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}

# Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00,  ns1=0.00000E+00,  E2=  structure(.Data=  c(3.92308E+00,  8.07692E+00,
2.40000E+01,  2.40000E+01,  1.44000E+02,  1.45000E+02),  .Dim=c(3,  2)),  t2=  structure(.Data=
c(1.00000E+00, 3.00000E+00, 1.00000E+00, 2.00000E+00, 1.00000E+00, 4.00000E+00), .Dim=c(3,
2)), r2= structure(.Data= c(9.00000E+00, 3.20000E+01, 3.60000E+01, 3.90000E+01, 1.19000E+02,
1.27000E+02), .Dim=c(3, 2)), time4= structure(.Data= c(1.00000E+00, 1.00000E+00, 1.00000E+00,
9.23077E-01, 9.23077E-01,    NA), .Dim=c(2, 3)), n4= structure(.Data= c(6.20000E+01, 6.60000E+01,
6.40000E+01, 7.80000E+01, 1.52000E+02,    NA), .Dim=c(2, 3)), t4= structure(.Data= c(1.00000E+00,
5.00000E+00, 7.00000E+00, 1.00000E+00, 6.00000E+00,    NA), .Dim=c(2, 3)), r4= structure(.Data=
c(5.50000E+01, 5.70000E+01, 5.60000E+01, 7.75000E+01, 1.48460E+02,       NA), .Dim=c(2, 3)),
ns2=3.00000E+00,    ns4=2.00000E+00,    na2=c(2.00000E+00,    2.00000E+00,    2.00000E+00),
na4=c(3.00000E+00, 2.00000E+00), nt=7.00000E+00, x= structure(.Data= c(  NA,  NA,  NA,  NA,
NA,       NA, 4.42308E-01, 3.19615E+01, 9.61538E-01, 5.31449E-01, 3.07692E-01, 8.45348E-01,
5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01,    NA,  NA,
NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA, 5.97015E-01, 2.88836E+01,
6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01, 5.39130E-01, 2.20609E+01, 9.00000E-01,
6.65217E-01, 9.23077E-01, 9.43478E-01,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,
NA,  NA,  NA, 5.53633E-01, 2.89983E+01, 8.47751E-01, 5.64014E-01, 1.00000E+00, 9.51557E-
01,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA,  NA), .Dim=c(3, 4,
6)), mx=c(5.36518E-01, 2.82643E+01, 8.21596E-01, 5.31449E-01, 7.46154E-01, 8.45348E-01),
r2.base=c(9.00000E+00,  3.60000E+01,  1.19000E+02),  E2.base=c(3.92308E+00,  2.40000E+01,
1.44000E+02),  r4.base=c(5.50000E+01,  7.75000E+01),  time4.base=c(1.00000E+00,  9.23077E-01),
n4.base=c(6.20000E+01, 7.80000E+01), ns2.base=3.00000E+00, ns4.base=2.00000E+00)


# Initial values (includes initial values for meta-regressions, which are redundant)
# Inits 1
```

```
list(B=5.00000E-01, d=c(          NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00,
1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00,
1.40000E+00, 1.40000E+00), mu4=c(5.00000E-01, 5.00000E-01))

# Inits 2
list(B=1.00000E-01, d=c(   NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01,
5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01,
7.00000E-01), mu4=c(2.50000E-01, 2.50000E-01))
```

Fixed effects model used for analyzing serious adverse events.

```
model{
        # Data type 2; r2 events in exposure E2
        # Poisson likelihood, log link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns2){                # LOOP THROUGH STUDIES
                mu2[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
                for (k in 1:na2[i]) {           # LOOP THROUGH ARMS
                        r2[i,k] ~ dpois(theta2[i,k])   # Poisson likelihood
                        theta2[i,k] <- lambda[i,k]*E2[i,k] # failure rate * exposure
                        # model for linear predictor
                        log(lambda[i,k]) <- mu2[i] + d[t2[i,k]] - d[t2[i,1]]
                        #Deviance contribution
                        dev2[i,k] <- 2*((theta2[i,k]-r2[i,k]) + r2[i,k]*log(r2[i,k]/theta2[i,k]))
                        }
                        #  summed residual deviance contribution for this trial
                        resdev2[i] <- sum(dev2[i,1:na2[i]])
                }
        totresdev2 <- sum(resdev2[])          #Total Residual Deviance

        # Data type 4; number of patients r4 out of n4 with >=1 event in time4
        # Binomial likelihood, cloglog link
        # Fixed effects model for multi-arm trials
        for(i in 1:ns4){                # LOOP THROUGH STUDIES
                mu4[i] ~ dnorm(0,.0001)         # vague priors for all trial baselines
                for (k in 1:na4[i]) {           # LOOP THROUGH ARMS
                        r4[i,k] ~ dbin(p[i,k],n4[i,k]) # Binomial likelihood
                        # model for linear predictor
                        cloglog(p[i,k]) <- log(time4[i,k]) + mu4[i] + d[t4[i,k]] - d[t4[i,1]]
                        rhat[i,k] <- p[i,k] * n4[i,k]        # expected value of the numerators
                        #Deviance contribution
                        dev4[i,k] <- 2 * (r4[i,k] * (log(r4[i,k])-log(rhat[i,k]))
                +  (n4[i,k]-r4[i,k]) * (log(n4[i,k]-r4[i,k]) - log(n4[i,k]-rhat[i,k])))        }
                        #  summed residual deviance contribution for this trial
                        resdev4[i] <- sum(dev4[i,1:na4[i]])
                }
        totresdev4 <- sum(resdev4[])          #Total Residual Deviance
totresdev<-totresdev2+totresdev4+0
        # Treatment effect model is shared between the three likelihoods
        d[1]<-0       # treatment effect is zero for control arm
        # vague priors for treatment effects
        for (k in 2:nt){  d[k] ~ dnorm(0,.0001) }
        for(k in 1:nt)
        {
                # Bayesian one-sided p-values
                # Probability that treatment j has higher hazard than treatment k
                # step(x) is 1 if x>=0
                for (j in 1:nt){ pval[j,k] <- step(d[j]-d[k]) }
        }
}
```

 # Data in BUGS format (some data is redundant)
list(ns5=0.00000E+00, ns1=0.00000E+00, E2= structure(.Data= c(2.40000E+01, 2.40000E+01, NA, 1.56164E+00, 3.36986E+00, NA, 6.92308E+00, 6.92308E+00, 6.00000E+00), .Dim=c(3, 3)), t2= structure(.Data= c(1.00000E+00, 2.00000E+00, NA, 1.00000E+00, 3.00000E+00, NA, 1.00000E+00, 4.00000E+00, 5.00000E+00), .Dim=c(3, 3)), r2= structure(.Data= c(2.00000E+00, 8.00000E+00, NA, 4.00000E+00, 8.00000E+00, NA, 6.00000E+00, 5.00000E+00, 6.00000E+00), .Dim=c(3, 3)), time4= structure(.Data= c(1.00000E+00, 1.00000E+00, 1.00000E+00, 9.23077E-01, 9.23077E-01, NA), .Dim=c(2, 3)), n4= structure(.Data= c(6.20000E+01, 6.60000E+01, 6.40000E+01, 7.80000E+01, 1.52000E+02, NA), .Dim=c(2, 3)), t4= structure(.Data= c(1.00000E+00, 6.00000E+00, 8.00000E+00, 1.00000E+00, 7.00000E+00, NA), .Dim=c(2, 3)), r4= structure(.Data= c(1.70000E+01, 1.70000E+01, 2.10000E+01, 6.79380E+01, 1.18864E+02, NA), .Dim=c(2, 3)), ns2=3.00000E+00, ns4=2.00000E+00, na2=c(2.00000E+00, 2.00000E+00, 3.00000E+00), na4=c(3.00000E+00, 2.00000E+00), nt=8.00000E+00, x= structure(.Data= c(NA, NA, NA, NA, NA, NA, 5.97015E-01, 2.88836E+01, 6.86567E-01, 4.17910E-01, 5.00000E-01, 5.67164E-01, 5.50505E-01, 2.80152E+01, 7.12121E-01, 6.21212E-01, 1.00000E+00, 9.19192E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 4.83871E-01, 3.24258E+01, 5.96774E-01, 5.23307E-01, 6.45161E-02, 7.39642E-01, 5.39130E-01, 2.20609E+01, 9.00000E-01, 6.65217E-01, 9.23077E-01, 9.43478E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, 5.40230E-01, 2.22448E+01, 7.23866E-01, 5.23307E-01, 2.30769E-01, 5.28736E-01, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA, NA), .Dim=c(3, 4, 6)), mx=c(5.42150E-01, 2.72162E+01, 7.23866E-01, 5.23307E-01, 5.43672E-01, 7.39642E-01), r2.base=c(2.00000E+00, 4.00000E+00, 6.00000E+00), E2.base=c(2.40000E+01, 1.56164E+00, 6.92308E+00), r4.base=c(1.70000E+01, 6.79380E+01), time4.base=c(1.00000E+00, 9.23077E-01), n4.base=c(6.20000E+01, 7.80000E+01), ns2.base=3.00000E+00, ns4.base=2.00000E+00)

 # Initial values (includes initial values for meta-regressions, which are redundant)
 # Inits 1
list(B=5.00000E-01, d=c(NA, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00, 1.00000E+00), sd=1.00000E+00, mu.base=1.00000E+00, mu2=c(1.40000E+00, 1.40000E+00, 1.40000E+00), mu4=c(5.00000E-01, 5.00000E-01))

 # Inits 2
list(B=1.00000E-01, d=c(NA, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01, 5.00000E-01), sd=5.00000E-01, mu.base=5.00000E-01, mu2=c(7.00000E-01, 7.00000E-01, 7.00000E-01), mu4=c(2.50000E-01, 2.50000E-01))

E.4 Pairwise results of the NMA

Table 9 Hazard ratios comparing all treatments on crisis*

Placebo	1.83 (1.45, 2.31)	3.48 (1.06, 13.60)	1.22 (1.06, 1.40)	1.49 (1.19, 1.85)	0.84 (0.64, 1.12)	1.03 (0.28, 3.88)	0.88 (0.33, 2.15)	0.97 (0.26, 3.49)	1.48 (0.55, 3.90)
0.55 (0.43, 0.69)	High-Dose Crizanlizumab	1.91 (0.57, 7.58)	0.67 (0.51, 0.88)	0.81 (0.63, 1.05)	0.46 (0.32, 0.67)	0.57 (0.15, 2.17)	0.48 (0.18, 1.21)	0.53 (0.14, 1.95)	0.81 (0.29, 2.18)
0.29 (0.07, 0.95)	0.52 (0.13, 1.76)	High-Dose NAC	0.35 (0.09, 1.16)	0.43 (0.11, 1.42)	0.24 (0.06, 0.82)	0.30 (0.04, 1.77)	0.25 (0.07, 0.74)	0.27 (0.04, 1.65)	0.42 (0.11, 1.32)
0.82 (0.71, 0.95)	1.50 (1.14, 1.97)	2.85 (0.86, 11.31)	L-glutamine	1.22 (0.94, 1.59)	0.69 (0.50, 0.95)	0.85 (0.23, 3.22)	0.72 (0.27, 1.79)	0.80 (0.21, 2.90)	1.21 (0.44, 3.22)
0.67 (0.54, 0.84)	1.23 (0.96, 1.59)	2.34 (0.70, 9.28)	0.82 (0.63, 1.07)	Low-Dose Crizanlizumab	0.57 (0.40, 0.81)	0.70 (0.18, 2.65)	0.59 (0.22, 1.48)	0.65 (0.17, 2.39)	1.00 (0.36, 2.65)
1.18 (0.89, 1.57)	2.17 (1.50, 3.13)	4.12 (1.22, 16.55)	1.45 (1.05, 1.99)	1.76 (1.23, 2.53)	senicapoc	1.23 (0.32, 4.75)	1.04 (0.38, 2.63)	1.15 (0.30, 4.29)	1.75 (0.62, 4.75)
0.97 (0.26, 3.63)	1.77 (0.46, 6.74)	3.39 (0.57, 22.44)	1.18 (0.31, 4.43)	1.44 (0.38, 5.47)	0.82 (0.21, 3.15)	High-Dose Senicapoc	0.84 (0.17, 4.19)	0.93 (0.25, 3.47)	1.42 (0.27, 7.25)

1.14 (0.46, 3.00)	2.09 (0.82, 5.65)	3.97 (1.36, 15.03)	1.39 (0.56, 3.68)	1.70 (0.68, 4.58)	0.97 (0.38, 2.62)	1.19 (0.24, 6.02)	Low-Dose NAC	1.11 (0.22, 5.61)	1.70 (0.71, 4.16)
1.03 (0.29, 3.88)	1.89 (0.51, 7.20)	3.65 (0.61, 23.66)	1.26 (0.34, 4.76)	1.54 (0.42, 5.86)	0.87 (0.23, 3.38)	1.08 (0.29, 3.97)	0.90 (0.18, 4.46)	Low-Dose Senicapoc	1.53 (0.30, 7.79)
0.68 (0.26, 1.83)	1.23 (0.46, 3.46)	2.36 (0.76, 8.95)	0.82 (0.31, 2.26)	1.00 (0.38, 2.80)	0.57 (0.21, 1.61)	0.70 (0.14, 3.67)	0.59 (0.24, 1.41)	0.65 (0.13, 3.35)	Mid-Dose NAC

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 10 Hazard ratios comparing all treatments on all-cause hospitalization days*

Placebo	1.72 (1.48, 2.00)	3.57 (1.85, 7.95)	2.97 (1.44, 6.35)	1.53 (1.12, 2.09)	1.00 (0.88, 1.14)
0.58 (0.50, 0.68)	High-Dose Crizanlizumab	2.08 (1.06, 4.66)	1.73 (0.82, 3.76)	0.89 (0.63, 1.26)	0.58 (0.50, 0.68)
0.28 (0.13, 0.54)	0.48 (0.21, 0.95)	Low-Dose NAC	0.83 (0.28, 2.28)	0.43 (0.18, 0.89)	0.28 (0.12, 0.55)
0.34 (0.16, 0.70)	0.58 (0.27, 1.22)	1.21 (0.44, 3.52)	L-glutamine	0.51 (0.23, 1.13)	0.34 (0.16, 0.71)

0.66 (0.48, 0.90)	1.13 (0.80, 1.58)	2.35 (1.13, 5.47)	1.95 (0.89, 4.41)	Mometasome	0.66 (0.47, 0.92)
1.00 (0.88, 1.14)	1.72 (1.48, 2.00)	3.57 (1.82, 8.03)	2.97 (1.42, 6.45)	1.52 (1.09, 2.14)	Low-Dose Crizanlizumab

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 11 Hazard ratios comparing all treatments on adverse events*

Placebo	0.92 (0.59, 1.46)	0.57 (0.25, 1.13)	0.94 (0.74, 1.21)	1.09 (0.70, 1.70)	1.42 (0.79, 2.97)	1.05 (0.67, 1.64)
1.08 (0.69, 1.71)	Low-Dose NAC	0.61 (0.25, 1.42)	1.02 (0.61, 1.72)	1.19 (0.62, 2.24)	1.56 (0.74, 3.66)	1.14 (0.60, 2.17)
1.77 (0.88, 4.01)	1.64 (0.70, 4.08)	Mometasome	1.67 (0.80, 3.86)	1.95 (0.84, 4.83)	2.55 (1.02, 7.58)	1.86 (0.80, 4.59)
1.06 (0.82, 1.36)	0.98 (0.58, 1.65)	0.60 (0.26, 1.25)	Senicapoc	1.16 (0.69, 1.91)	1.51 (0.80, 3.30)	1.11 (0.67, 1.86)
0.91 (0.59, 1.43)	0.84 (0.45, 1.60)	0.51 (0.21, 1.19)	0.86 (0.52, 1.44)	High-Dose Crizanlizumab	1.31 (0.62, 3.08)	0.96 (0.61, 1.48)
0.70 (0.34, 1.26)	0.64 (0.27, 1.36)	0.39 (0.13, 0.98)	0.66 (0.30, 1.25)	0.76 (0.32, 1.60)	L-glutamine	0.73 (0.31, 1.53)
0.95 (0.61, 1.50)	0.88 (0.46, 1.68)	0.54 (0.22, 1.25)	0.90 (0.54, 1.50)	1.04 (0.67, 1.63)	1.37 (0.65, 3.21)	Low-Dose Crizanlizumab

***** *Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.*

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 12 Hazard ratios comparing all treatments on serious adverse events*

Placebo	0.22 (0.03, 0.92)	1.04 (0.27, 3.36)	1.22 (0.35, 4.39)	0.88 (0.27, 2.85)	1.08 (0.54, 2.14)	1.34 (0.95, 1.89)	0.80 (0.42, 1.53)
4.50 (1.08, 37.94)	Low-Dose NAC	4.67 (0.68, 50.13)	5.70 (0.81, 63.02)	4.05 (0.59, 43.70)	4.92 (1.00, 42.52)	6.05 (1.40, 50.86)	3.66 (0.75, 31.45)
0.96 (0.30, 3.64)	0.21 (0.02, 1.48)	Prasugrel	1.19 (0.22, 7.18)	0.85 (0.16, 4.95)	1.04 (0.27, 4.55)	1.30 (0.38, 5.12)	0.78 (0.20, 3.32)
0.82 (0.23, 2.82)	0.18 (0.02, 1.24)	0.84 (0.14, 4.63)	High-Dose Ticagrelor	0.72 (0.20, 2.42)	0.87 (0.21, 3.69)	1.10 (0.29, 3.97)	0.65 (0.16, 2.66)
1.14 (0.35, 3.75)	0.25 (0.02, 1.69)	1.18 (0.20, 6.24)	1.40 (0.41, 5.00)	Low-Dose Ticagrelor	1.23 (0.32, 4.86)	1.53 (0.45, 5.28)	0.92 (0.24, 3.52)
0.93 (0.47, 1.87)	0.20 (0.02, 1.00)	0.96 (0.22, 3.74)	1.14 (0.27, 4.81)	0.81 (0.21, 3.17)	High-Dose Crizanlizumab	1.24 (0.58, 2.70)	0.75 (0.39, 1.43)

0.74 (0.53, 1.05)	0.17 (0.02, 0.71)	0.77 (0.20, 2.64)	0.91 (0.25, 3.41)	0.65 (0.19, 2.22)	0.80 (0.37, 1.72)	L-glutamine	0.60 (0.29, 1.24)
1.24 (0.65, 2.40)	0.27 (0.03, 1.33)	1.29 (0.30, 4.95)	1.54 (0.38, 6.35)	1.09 (0.28, 4.20)	1.34 (0.70, 2.58)	1.67 (0.81, 3.47)	Low-Dose Crizanlizumab

* Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

Table 13 Hazard ratios comparing all treatments on crisis using >18 year old subgroup results from Niihara 2018*

Placebo	1.83 (1.44, 2.32)	3.49 (1.09, 13.48)	1.56 (1.11, 2.19)	1.48 (1.19, 1.86)	0.85 (0.64, 1.12)	1.02 (0.28, 3.75)	0.88 (0.34, 2.10)	0.97 (0.26, 3.52)	1.47 (0.55, 3.90)
0.55 (0.43, 0.69)	High-Dose Crizanlizumab	1.91 (0.58, 7.46)	0.86 (0.57, 1.29)	0.81 (0.63, 1.05)	0.46 (0.32, 0.67)	0.56 (0.15, 2.10)	0.48 (0.18, 1.18)	0.53 (0.14, 1.96)	0.81 (0.29, 2.20)
0.29 (0.07, 0.92)	0.52 (0.13, 1.72)	High-Dose NAC	0.45 (0.11, 1.52)	0.43 (0.11, 1.40)	0.24 (0.06, 0.81)	0.29 (0.04, 1.66)	0.25 (0.07, 0.74)	0.27 (0.04, 1.60)	0.42 (0.11, 1.32)
0.64 (0.46, 0.90)	1.17 (0.77, 1.77)	2.24 (0.66, 8.93)	L-glutamine	0.95 (0.63, 1.43)	0.54 (0.35, 0.84)	0.65 (0.17, 2.51)	0.56 (0.20, 1.43)	0.62 (0.16, 2.35)	0.94 (0.33, 2.66)

0.67 (0.54, 0.84)	1.23 (0.96, 1.59)	2.35 (0.71, 9.19)	1.05 (0.70, 1.58)	Low-Dose Crizanlizumab	0.57 (0.40, 0.81)	0.69 (0.18, 2.57)	0.59 (0.22, 1.45)	0.65 (0.17, 2.43)	0.99 (0.37, 2.69)
1.18 (0.89, 1.57)	2.16 (1.50, 3.12)	4.14 (1.23, 16.30)	1.85 (1.19, 2.88)	1.76 (1.23, 2.51)	Senicapoc	1.21 (0.32, 4.58)	1.04 (0.38, 2.60)	1.14 (0.30, 4.29)	1.75 (0.62, 4.79)
0.98 (0.27, 3.61)	1.79 (0.48, 6.83)	3.45 (0.60, 22.24)	1.53 (0.40, 5.91)	1.45 (0.39, 5.48)	0.82 (0.22, 3.14)	High-Dose Senicapoc	0.86 (0.18, 4.13)	0.94 (0.25, 3.47)	1.43 (0.28, 7.35)
1.13 (0.48, 2.94)	2.08 (0.85, 5.48)	3.98 (1.35, 14.62)	1.77 (0.70, 4.89)	1.68 (0.69, 4.45)	0.96 (0.38, 2.61)	1.17 (0.24, 5.71)	Low-Dose NAC	1.10 (0.23, 5.49)	1.68 (0.72, 4.17)
1.04 (0.28, 3.84)	1.89 (0.51, 7.17)	3.66 (0.63, 23.10)	1.63 (0.43, 6.32)	1.54 (0.41, 5.82)	0.88 (0.23, 3.39)	1.07 (0.29, 3.93)	0.91 (0.18, 4.36)	Low-Dose Senicapoc	1.53 (0.30, 7.76)
0.68 (0.26, 1.81)	1.24 (0.46, 3.41)	2.36 (0.76, 9.08)	1.06 (0.38, 3.00)	1.01 (0.37, 2.73)	0.57 (0.21, 1.60)	0.70 (0.14, 3.53)	0.60 (0.24, 1.39)	0.65 (0.13, 3.31)	Mid-Dose NAC

***** Pairwise hazard ratios of row vs. column; values below 1 in, for example, the high-dose crizanlizumab row suggest lower hazard of event on crizanlizumab than on comparator.

High-Dose Ticagrelor=twice daily 45mg, Low-Dose Ticagrelo=twice daily 10mg; Low-Dose NAC= N-acetylcysteine 600mg, Mid-Dose NAC=N-acetylcysteine 1200mg, High-Dose NAC= N-acetylcysteine 2400mg; Senicapoc=loading dose of 20mg twice daily for 4 days followed by 10mg daily maintenance, Low-Dose Senicapoc=single loading dose of 100mg followed by maintenance 6mg daily, High-Dose Senicapoc=single loading dose of 150mg followed by maintenance 10mg daily.

E.5 Cumulative ranking plots - Rankograms

In this appendix we provide the cumulative ranking plots, which are called 'rankograms'. These are the cumulative probability that each treatment is in the top 1, 2, 3, … treatments on the basis of each outcome.

Figure 3 Cumulative ranking plot for Crisis

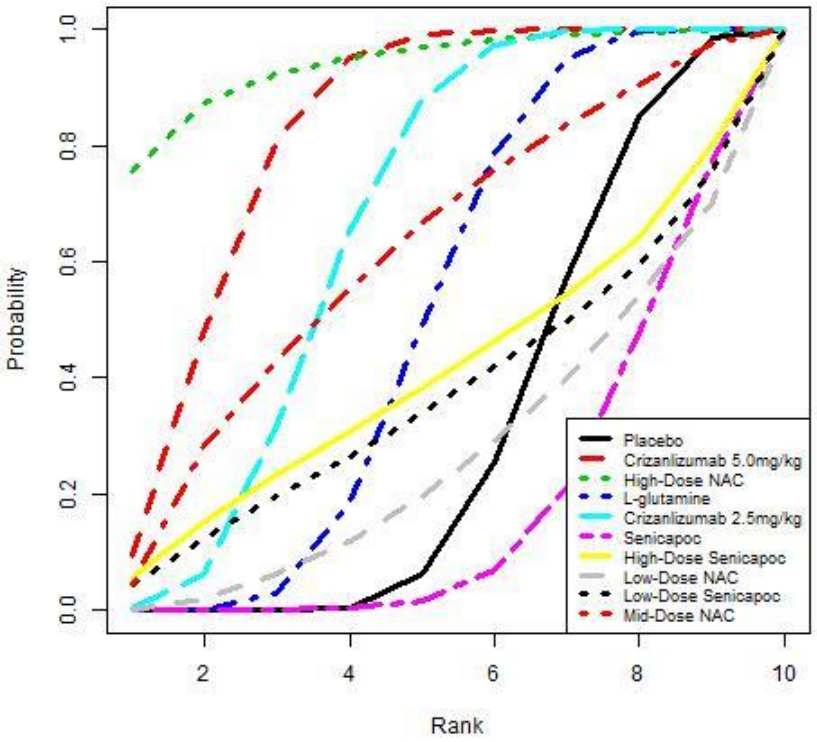


Figure 4 Cumulative ranking plot for adverse events

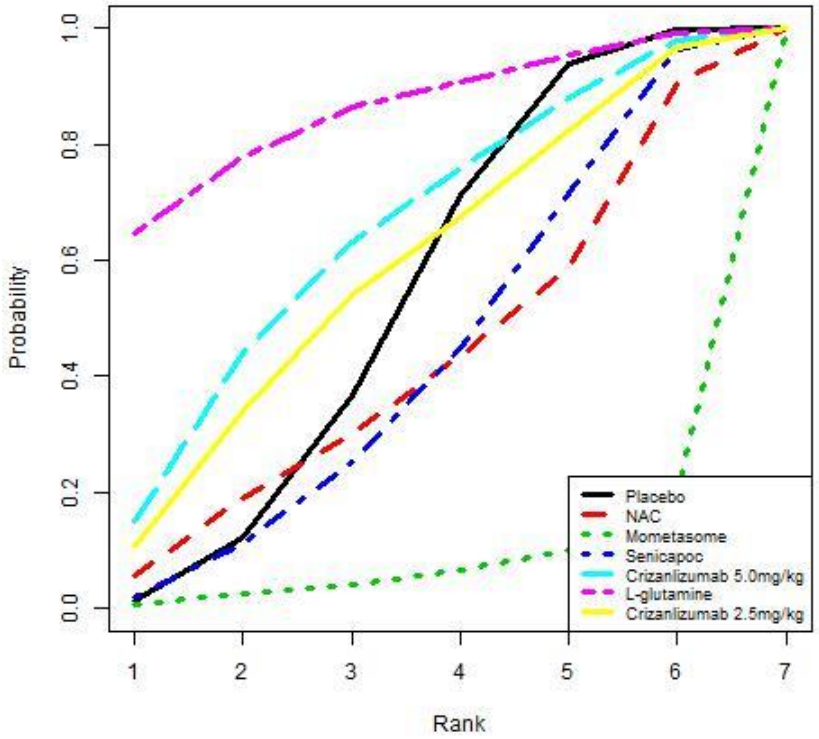

Probability
0.0
0.2
0.4
0.6
0.8
1.0
1
2
3
4
5
6
7
Rank
Placebo
NAC
Mometasome
Senicapoc
Crizanlizumab 5.0mg/kg
L-glutamine
Crizanlizumab 2.5mg/kg

Figure 5 Cumulative ranking plot for serious adverse events

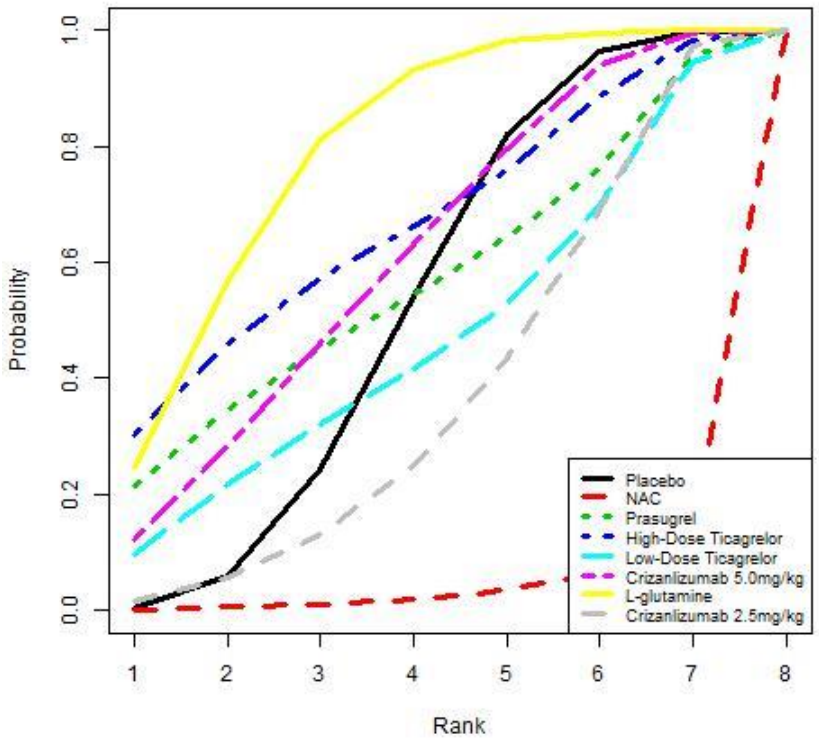
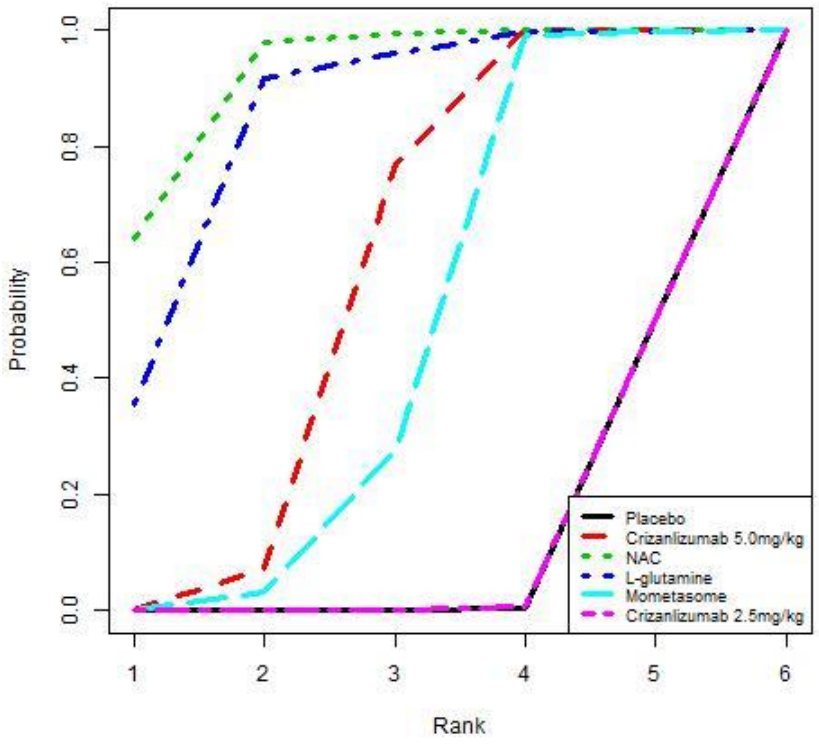


Figure 6 Cumulative ranking plot for all-cause hospitalization days



E.6 Sensitivity analysis using precise priors on treatment and baseline effects

A sensitivity analysis was conducted using a more precise prior on the baseline and treatment effects (i.e. $\mu_{..}$ and $d_{..}$, respectively). Instead of the base case priors of $Normal(0, 0.0001)$ we used $Normal(0, 0.1)$. The forest plot of results is in Figure 7 and the Bayesian probabilities of superiority (along with a comparison with base case results) are presented in Table 14. There is very limited impact on the results so our results are likely robust to prior assumptions.

Figure 7. Forest plot of all outcomes using more precise prior distributions

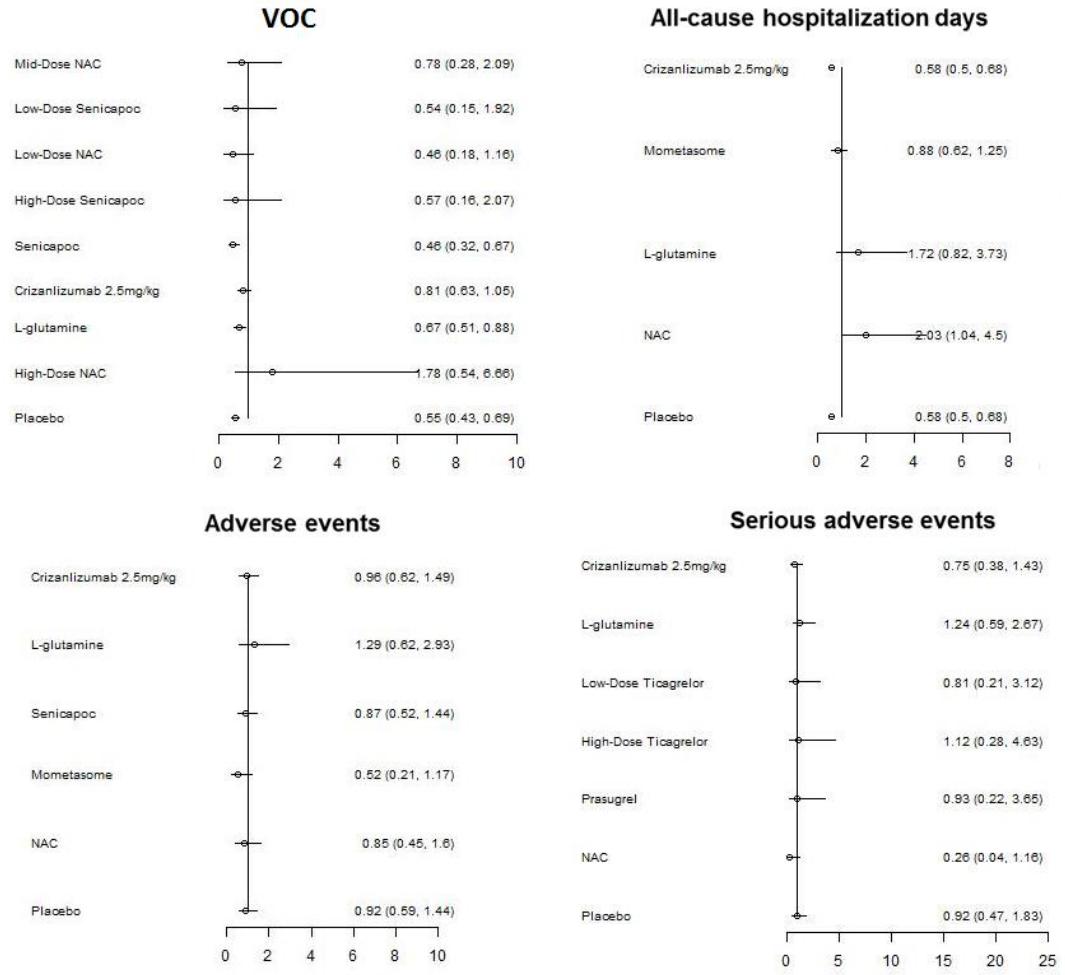


Table 14 Bayesian probabilities that crizanlizumab is superior on each outcome analyzed using both the precise prior sensitivity analysis and the vague priors of the base case*

	VOC	All-cause hospitalization	Adverse events	Serious adverse events	VOC	All-cause hospitalization	Adverse events	Serious adverse events
Placebo	>0.9999	>0.9999	0.6384	0.5895	>0.9999	>0.9999	0.6558	0.5857
L-glutamine	0.9982	0.0747	0.2563	0.2847	0.9982	0.0731	0.2480	0.2854
Crizanlizumab 2.5mg/kg	0.9425	>0.9999	0.5772	0.8136	0.9452	>0.9999	0.5743	0.8134
Mometasome	-	0.7548	0.9408	-	-	0.7496	0.9399	-
Low-Dose NAC	0.9486	0.0193	0.6978	0.9601	0.9396	0.0166	0.6996	0.9744
Mid-Dose NAC	0.6919	-	-	-	0.6619	-	-	-
High-Dose NAC	0.1720	-	-	-	0.1507	-	-	-
Prasugrel	-	-	-	0.5398	-	-	-	0.5242
Senicapoc	>0.9999	-	0.7038	-	>0.9999	-	0.7176	-

High-Dose Senicapoc	0.8077	-	-	-	0.8010	-	-	-
Low-Dose Senicapoc	0.8328	-	-	-	0.8334	-	-	-
High-dose Ticagrelor	-	-	-	0.4380	-	-	-	0.4247
Low-dose Ticagrelor	-	-	-	0.6267	-	-	-	0.6181

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