Supplementary Data 1: Risk of Bias assessed with ROBINS-I

Study	Domain 1	Domain 2	Domain 3	Domain 4	Domain 5	Domain 6	Domain 7	Overall
Hagen et al., 2007	Low	Moderate	Moderate	Low	Low	Moderate	Moderate	Moderate
Hagen et al., 2011	Low	Serious	Moderate	Low	Moderate	Moderate	Moderate	Serious

Table S1: Report of the consensus of the risk of bias with Risk Of Bias In Non-Randomized Studies of Interventions (ROBINS-I) tool evaluated by two authors. Domain 1: Bias due to confounding, Domain 2: Bias in selection of participants into the study, Domain 3: Bias in classification of interventions, Domain 4: Bias due to deviations from intended interventions, Domain 5: Bias due to missing data, Domain 6: Bias in measurement of outcomes, Domain 7: Bias in selection of the reported result.

Supplementary Data 2: Code used in R for the meta-analysis

META-ANALYSIS 1, EFFICACY:

```
dat1 <- escalc(measure="OR", ai=dat.bcg$`TTX responders`, bi=dat.bcg$`TTX non-responders`,
ci=dat.bcg$`Placebo responders`, di=dat.bcg$`Placebo non-responders`, data=dat.bcg)
dat1
```

```
          Author Year TTX.responders TTX.non.responders Placebo.responders Placebo.non.responders
yi     vi
1    Hagen et al., 2017          33              32              29                   55 0.6708 0.1142
2 Goldlust et al., 2021          15              11               8                   17 1.0639 0.3414
3    Hagen et al., 2008          16              25              12                   29 0.4361 0.2203
```

```
res1 <- rma(yi, vi, data=dat1)
Res1
confint(res1)
```

```
      estimate  ci.lb   ci.ub
tau^2    0.0000 0.0000  3.6863
tau      0.0000 0.0000  1.9200
I^2(%)   0.0000 0.0000 94.7028
H^2      1.0000 1.0000 18.8777
```

```
> res1
Random-Effects Model (k = 3; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 0.1980)
tau (square root of estimated tau^2 value):      0
I^2 (total heterogeneity / total variability):   0.00%
H^2 (total variability / sampling variability):  1.00
```

Test for Heterogeneity:
Q(df = 2) = 0.7023, p-val = 0.7039

Model Results:

estimate se zval pval ci.lb ci.ub
0.6761 0.2483 2.7233 0.0065 0.1895 1.1627 **

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1

forest(res1, xlim=c(-1.8,4), annotate=TRUE, showweights=TRUE, col = "green", border = "black", cex=1.6, order="obs", header="Author(s), Year", slab=paste(dat.bcg$Author, dat.bcg$Year, sep=", "))

META-ANALYSIS 2, >1 AE RELATED TO THE DRUG:

Author	Year	TTX AE	TTX NON-AE	PLACEBO AE	PLACEBO NON-AE
Hagen et al.,	2017	77	0	77	11
Goldlust et al.,	2021	9	17	3	22
Hagen et al.,	2008	34	7	28	12

datAE <- escalc(measure="OR", ai=X_1_AE_related_to_the_drug$`TTX AE`, bi=X_1_AE_related_to_the_drug$`TTX NON-AE`, ci=X_1_AE_related_to_the_drug$`PLACEBO AE`, di=X_1_AE_related_to_the_drug$`PLACEBO NON-AE`, data=X_1_AE_related_to_the_drug)
> dat1

Author Year TTX.responders TTX.non.responders Placebo.responders Placebo.non.responders yi vi
1 Hagen et al., 2017 33 32 29 55 0.6708 0.1142
2 Goldlust et al., 2021 15 11 8 17 1.0639 0.3414
3 Hagen et al., 2008 16 25 12 29 0.4361 0.2203

> resAE=rma(datAE$yi, datAE$vi, data=datAE)
> resAE

Random-Effects Model (k = 3; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0.0000 (SE = 0.5672)
tau (square root of estimated tau^2 value): 0.0026
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 2) = 2.5377, p-val = 0.2812

forest(resAE, annotate=TRUE, showweights=TRUE, col = "red", border = "black", cex=1.6, order="obs", header="Author(s), Year", slab=paste(X_1_AE_related_to_the_drug$Author, X_1_AE_related_to_the_drug$Year, sep=", "))

META-ANALYSIS 3, SERIOUS ADVERSE EVENTS RELATED TO THE DRUG

SAE_related_to_the_drug <- read_excel("C:/Users/ASUS/Downloads/SAE related to the drug.xlsx")
> View(SAE_related_to_the_drug)
> datSAE <- escalc(measure="OR", ai=SAE_related_to_the_drug$`TTX SAE`, bi=SAE_related_to_the_drug$`TTX NON-SAE`, ci=SAE_related_to_the_drug$`PLACEBO SAE`, di=SAE_related_to_the_drug$`PLACEBO NON-SAE`, data=SAE_related_to_the_drug)
> datSAE

	Author	Year	TTX.SAE	TTX.NON.SAE	PLACEBO.SAE	PLACEBO.NON.SAE	yi	vi
1	Hagen et al.,	2017	6	71	3	85	0.8731	0.5258
2	Goldlust et al.,	2021	1	25	1	24	-0.0408	2.0817
3	Hagen et al.,	2008	1	40	0	41	1.1230	2.7155

resSAE=rma(datAE$yi, datAE$vi, data=datAE)
> resSAE
Random-Effects Model (k = 3; tau^2 estimator: REML)

tau^2 (estimated amount of total heterogeneity): 0 (SE = 1.4420)
tau (square root of estimated tau^2 value): 0
I^2 (total heterogeneity / total variability): 0.00%
H^2 (total variability / sampling variability): 1.00

Test for Heterogeneity:
Q(df = 2) = 0.3805, p-val = 0.8268

Model Results:

estimate	se	zval	pval	ci.lb	ci.ub
0.7469	0.6030	1.2387	0.2154	-0.4349	1.9288

Signif. codes: 0 ‘***’ 0.001 ‘**’ 0.01 ‘*’ 0.05 ‘.’ 0.1 ‘ ’ 1