Efficacy, safety, and comparison of sonic hedgehog inhibitors in basal cell carcinomas: A systematic review and meta-analysis

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Background: Sonic hedgehog inhibitors (SHHis) provide an additional treatment option for basal cell carcinomas (BCCs), especially for metastatic or locally advanced BCC. However, studies have been heterogeneous and lacked direct comparisons between molecules.

Objective: To determine the efficacy and safety of the class of molecules SHHi for treating BCC and to compare them individually.

Methods: We performed a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses)—compliant systematic review of studies followed by a meta-analysis.

Results: Eighteen articles were included in our meta-analysis; 16 articles were combined for efficacy and 16 for safety. In locally advanced BCC, overall response rates (ORRs) were similar for vismodegib and sonidegib (69% vs 57%, respectively) but not complete response rates (31% vs 3%, respectively). In metastatic disease, the ORR of vismodegib was 2.7-fold higher than the ORR of sonidegib (39% vs 15%, respectively). For side effects affecting a majority of patients, prevalences for muscle spasms (67.1%), dysgeusia (54.1%), and alopecia (57.7%) were in similar proportions for sonidegib and vismodegib. Patients receiving sonidegib experienced more upper gastrointestinal distress than patients receiving vismodegib.

Conclusion: SHHis induce a partial response to locally advanced BCC disease. Side effects are common, similar across molecules, associated with high discontinuation rates, and warrant discussion beforehand. (J Am Acad Dermatol 2018;79:1089-100.)

Key words: alopecia; basal cell carcinoma; dysgeusia; itraconazole; meta-analysis; muscle spasms; sonic hedgehog inhibitors; sonidegib; TAK-441; vismodegib.

Nonmelanoma skin cancers affect ~3.5 million Americans yearly, most of which are basal cell carcinomas (BCCs), the most common malignancy.[1] The incidence of BCC has steadily increased, with a lifetime risk approaching 30% in white persons.[2] In 2016, a large retrospective US study estimated that locally advanced BCC (laBCC) and metastatic BCC (mBCC) account for 0.8% and 0.04% of all BCC, respectively.[3] laBCC has no formal definition but is described as a large destructive lesion that relapsed after radiation therapy or for which radiotherapy is contraindicated that is inoperable or unsuitable for surgery (because of location, patient, or morbidity).[4] Age-adjusted incidence rates were 1.83 cases/100,000 persons and 0.04 cases/100,000 persons for laBCC and mBCC, respectively.[3] Median overall survival is 78.8 months for laBCC[5] and 10 months for mBCC.[6] Death occurs

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Drs Xie and Lefrançois contributed to this work equally.
Funding sources: Partly supported by the Canadian Dermatology Foundation.
Conflicts of interest: None disclosed.
Accepted for publication July 3, 2018.
Reprints not available from the authors.

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Published online July 10, 2018.
0190-9622/$36.00

https://doi.org/10.1016/j.jaad.2018.07.004

either from aggressive invasion of organs, such as the brain,[7] or from proliferation of distant metastases.

Insights into targeted therapies came from deciphering the molecular pathway leading to nevoid BCC syndrome, or Gorlin-Goltz syndrome.[8] Gorlin-Goltz syndrome is caused most commonly, but not exclusively, by mutations in *PTCH* (patched), the main receptor in the sonic hedgehog (SHH) pathway for the SHH ligand.[9] Unbound, PTCH acts as an inhibitor for the pathway by inhibiting the downstream transmembrane receptor SMO (smoothened); after binding SHH ligand, PTCH is inactivated and SMO signaling becomes active, enabling transcription factor–mediated (GLI family) gene expression of the SHH pathway targets.[10] Molecular therapies that downregulate SHH pathway signaling to impede BCC tumorigenesis are currently available (SMO inhibitors) or under development (GLI inhibitors). They together belong to the class sonic hedgehog inhibitors (SHHis).[11]

CAPSULE SUMMARY

- Sonic hedgehog inhibitors are systemic treatments for locally advanced and metastatic basal cell carcinomas.
- In locally advanced disease, the overall response rate is similarly significant for sonidegib and vismodegib, and the complete response rate is significant for vismodegib only. Rates of major side effects do not differ between vismodegib and sonidegib.
- Patients should expect partial responses in locally advanced disease.

For mBCC and laBCC not amenable to radiotherapy or surgery, SHHis constitute the major treatment option.[12] Two oral SHHis, both SMO inhibitors, have been approved by the Food and Drug Administration: vismodegib in 2012 (for laBCC and mBCC) and sonidegib in 2015 (for laBCC). Both medications were approved without undergoing phase 3 randomized clinical trials (RCTs): vismodegib under priority review as a first-in-class molecule and sonidegib because of promising and durable phase 2 results and the need for alternative molecules.[13] For vismodegib, a phase 2 nonplacebo–controlled prospective cohort study (ERIVANCE) showed overall response rates (ORRs) of 50% for laBCC and 34% for mBCC.[4] For sonidegib, a phase 2 nonplacebo–controlled RCT (BOLT) showed an ORR of 57% for laBCC and 15% for mBCC.[14] Since Food and Drug Administration approval, other studies have started to emerge that are typically underpowered, not placebo-controlled, and heterogeneous (eg, differences in study populations, outcomes, designs, sample sizes). Other potential SHHi molecules have been evaluated for treating BCC, such as TAK-441[15] and itraconazole, an azole antifungal with mild SHH pathway inhibition.[16]

A previous systematic review focused on available data for vismodegib.[13] It provided weighted means for efficacy and major side effects but excluded other SHHis and did not use statistical methods to account for different study sizes (~100-fold variation).[13] In our systematic review and meta-analysis, we aimed to determine the efficacy and safety of SHHi as a class and the similarities and differences among the different molecules in this class.

METHODS

Systematic review

This systematic review and meta-analysis followed PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.[17] The study protocol was published prospectively by GitHub Inc (https://github.com/plefrancois/Meta_BCC_SHHi). Our search goal was to retrieve all studies involving the treatment of BCC with SHHis. We used ClinicalTrials.gov to determine which SHHis had been used to treat BCC. We performed a broad search in PubMed, ClinicalTrials.gov, Embase, and Cochrane Central Register of Clinical Trials using key words "basal cell carcinoma," "BCC," "vismodegib," "Erivedge," "sonidegib," "odomzo," "itraconazole," and "TAK-441" for articles published before the end of 2016. In total, 308 articles were screened independently by both authors. We narrowed the list to include clinical trials, prospective case series, and retrospective medical record reviews on human subjects written in English. We excluded case reports, studies providing only outcomes after surgery or radiotherapy, studies of SHHis used concurrently with additional treatments, and studies without quantitative measurements. Full-length publications were then evaluated for the aforementioned criteria. In the end, we included 18 studies: 14 studies assessing both efficacy and safety, 2 studies assessing efficacy only, and 2 studies assessing safety only.

Two investigators extracted data independently using a standardized Excel form. Variables included study size, medication, median follow-up and drug exposure in months, response rates, type of response (central and independent review favored), and adverse event rates. Quality of evidence was assessed by using Oxford Center for Evidence-Based Medicine levels. Biases were reviewed individually by the 2 investigators followed by joint evaluation.

Abbreviations used:

BCC:	basal cell carcinoma
CBR:	clinical benefit rate
CI:	confidence interval
CRR:	complete response rate
laBCC:	locally advanced basal cell carcinoma
mBCC:	metastatic basal cell carcinoma
ORR:	overall response rate
PTCH:	patched
RCT:	randomized clinical trial
RECIST:	response evaluation criteria in solid tumors
SCC:	squamous cell carcinoma
SHH:	sonic hedgehog
SHHis:	sonic hedgehog inhibitors
SMO:	smoothened

One disagreement was the cut-off between large and small studies, which was settled at ≥50 patients for large studies.

Meta-analysis

Among the 18 studies included in the systematic review, 16 (1102 patients total) were analyzed for assessing efficacy. Overall response rates (ORRs) and complete response rates (CRRs) were the primary outcomes. ORR was defined as the proportion of patients with either a partial or complete response after treatment. CRR represents the percentage of patients with a complete response. Clinical benefit rates (CBRs) were secondary outcomes and represented the proportion of patients with stable disease plus any responders. All response rates were similarly computed across different studies. However, methods of outcome assessment varied. To assess safety, in up to 16 studies (1486 patients total), we analyzed the prevalence of the following common side effects: dysgeusia (ie, dysfunction in sense of taste), muscle spasms, alopecia, fatigue, nausea, weight loss, diarrhea, decreased appetite, skin squamous cell carcinoma (SCC), myalgias, vomiting, amenorrhea, and increased creatine kinase. Data from multiple dosing regimens were merged.

Studies were heterogeneous in their designs and population sizes. Most studies did not provide variance or data needed to calculate variance. To standardize comparisons for meta-analysis pooling, we considered relative per-study sampling variances equal to $1/\sqrt{\text{population size}}$, thus giving more weight to larger studies. Analyses were performed in R. Data were pooled using linear models with fixed-effects meta-analysis for primary analyses, along with 95% confidence intervals (CIs) and *P* values. Comparisons to Bayesian models with random-effects meta-analysis were performed as sensitivity analyses. Publication bias was assessed by using funnel plots and the trim-and-fill method, which determines asymmetry in metrics from individual studies and generates additional missing trials to correct for this bias.[18] Heterogeneity was assessed by forest plots and the I^2 statistic.

RESULTS

Systematic review

This study's flow diagram is shown in Supplemental Fig 1 (available at http://www.jaad.org). Fourteen studies focused on vismodegib,[4,12,19-32] 2 on sonidegib,[14,33,34] 1 on itraconazole,[16] and 1 on TAK-441.[15] Table I presents efficacy data and Table II safety data for individual studies. Across all studies, median drug exposure ranged 1.3-21 (median 5.25) months and median follow-up time 1.3-36 (median 11) months.

Bias assessment

Among the 18 studies, 13 were industry-sponsored. These 13 studies provided 95.8% of the patients included in the meta-analysis. Study size was heterogeneous, ranging 5-499 SHHi-exposed patients in the individual studies. Seven studies included ≥50 SHHi-exposed patients, 15 studies lacked a placebo arm, and 4 studies were double-blinded. Response criteria used for assessment varied: 2 studies used centrally-assessed response evaluation criteria in solid tumors (RECIST), 6 investigator-based RECIST, 1 used a mixed design (RECIST plus clinical outcomes), 1 histopathologic clearance, 5 clinical outcome, and 1 did not provide information. Although we assessed publication bias quantitatively, all studies showed a minimum partial response (Table I).

Efficacy of SHHi

The 16 studies listed in Table I were pooled by using fixed-effects linear models to analyze efficacy.* Pooled ORR for all patients was 59.6% (95% CI 40.3%-78.9%; forest plot, Fig 1, *A*), indicating that most patients receiving SHHis achieve at least a partial response ($z = 6.14$; $P < .0001$). As a sensitivity analysis, Bayesian models with random effects showed an ORR of 58.5% (95% CI 36.5%-79.4%; Supplemental Fig 2; available at http://www.jaad.org). The I^2 test for heterogeneity was negative, but ORRs estimated from individual studies tend to be imprecise; because most studies did not provide measurements of dispersion, we calculated conservative estimates on the basis of the study size. Without altering results, we assessed publication

*[4,12,14-16,19-30,33,34]

Table I. Efficacy of SHHi and study characteristics

Study name	Study type	Quality of evidence*	Molecule	Response criteria	Patients, N	ORR, %	CRR, %	CBR, %
BOLT[14,34]	Double-blinded RCT, no placebo	2	Sonidegib	Central RECIST	200	49.5	2.5	98.5
Viscusi, 2015[19]	Prospective case series	4	Vismodegib	Unknown	24	95.8	54.2	100.0
Tauber, 2015[20]	Prospective case series	4	Vismodegib	Investigator RECIST	7	57.1	0	100.0
STEVIE[21]	Open-label, multicenter, single-arm clinical trial	2	Vismodegib	Investigator RECIST	456	68.6	34.0	96.7
ERIVANCE[4,22]	Prospective cohort study (2 cohorts)	2	Vismodegib	Central RECIST	92	44.6	15.2	90.2
Ozgur, 2015[23]	Retrospective case reviews	4	Vismodegib	Investigator RECIST	12	66.7	16.7	83.3
Sofen_2015[24]	Open-label, nonrandomized 3-arm clinical trial	2	Vismodegib	Histology	65	38.5	38.5	95.4
Demirci, 2015[25]	Retrospective case reports	4	Vismodegib	Investigator RECIST	6	100.0	33.3	100.0
Kim, 2014[16]	Open-label, nonrandomized 3-arm clinical trial with placebo	2	Itraconazole	Clinical	8	50.0	0	NA
EAS[26]	Open-label, nonrandomized 2-cohort, single-arm clinical trial	2	Vismodegib	Investigator RECIST	88	43.2	9.1	96.6
Gill, 2013[27]	Prospective case series	4	Vismodegib	Clinical	5	100.0	40.0	100.0
Von Hoff LoRusso[12,28]	Phase 1 trial	2	Vismodegib	Mixed	33	54.5	6.1	87.9
Simone, 2016[29]	Prospective case series	4	Vismodegib	Clinical	6	66.7	16.7	66.7
NCT01350115[33]	Phase 2 double-blinded RCT, with placebo	1	Sonidegib	Clinical	7	85.7	42.9	100.0
RegiSONIC[30]	Prospective cohort	2	Vismodegib	Clinical	88	69.3	47.7	NA
Goldman, 2015[15]	Phase 1 trial	2	TAK-441	Investigator RECIST	5	20.0	0	100.0

CBR, Clinical benefit rate; *CRR*, complete response rate; *EAS*, expanded access study; *NA*, not available or ascertained; *ORR*, overall response rate; *RCT*, randomized clinical trial; *RECIST*, response evaluation criteria in solid tumors; *SHHi*, sonic hedgehog inhibitor.

*Quality of evidence assessed per Oxford Centre for Evidence-based Medicine.

Table II. Prevalence of major side effects of SHHi

Study name	Study type	Quality of evidence*	Molecule	Response criteria	Patients, N	Muscle spasm, %	Dysgeusia, %	Alopecia, %	Weight loss, %	Fatigue, %	Nausea, %	Myalgia, %	Vomiting, %	Skin SCC, %	Increased CK, %	Diarrhea, %	Decreased appetite, %	Amenorrhea, %†
BOLT[14,34]	Double-blinded RCT, no placebo	2	Sonidegib	Central RECIST	229	63.3	53.3	54.6	37.6	33.6	41.0	23.6	20.5	NA	10.9	25.3	28.8	NA
Viscusi, 2015[19]	Prospective case series	4	Vismodegib	Unknown	22	54.5	59.1	54.5	36.4	31.8	NA	NA	NA	4.5	NA	NA	NA	NA
Tauber, 2015[20]	Prospective case series	4	Vismodegib	Investigator RECIST	7	100.0	71.4	42.9	NA	NA	NA	NA	NA	28.6	NA	NA	NA	NA
STEVIE[21]	Open-label, multicenter, single-arm clinical trial	2	Vismodegib	Investigator RECIST	499	63.5	53.9	61.5	32.5	16.0	16.0	7.8	NA	1.0	NA	16.6	25.3	27.6 (29)
ERIVANCE[4,22]	Prospective cohort study (2 cohorts)	2	Vismodegib	Central RECIST	104	74.0	55.8	68.3	51.9	42.3	33.7	NA	NA	NA	NA	26.9	27.9	33.3 (6)
Ozgur, 2015[23]	Retrospective case reviews	4	Vismodegib	Investigator RECIST	12	100.0	75.0	75.0	83.3	33.3	25.0	16.7	0.0	NA	NA	16.7	41.7	NA
Sofen, 2015[24]	Open-label, nonrandomized, 3-arm clinical trial	2	Vismodegib	Histology	74	75.7	50.0	58.1	NA	20.3	17.6	NA	NA	NA	NA	8.1	10.8	NA
Demirci, 2015[25]	Retrospective case reports	4	Vismodegib	Investigator RECIST	8	75.0	25.0	50.0	NA	NA	NA	NA	NA	NA	NA	12.5	NA	NA
EAS[26]	Open-label, nonrandomized, 2-cohort, single-arm clinical trial	2	Vismodegib	Investigator RECIST	119	70.6	70.6	58.0	16.0	19.3	19.3	NA	NA	0.8	NA	25.2	NA	50.0 (8)
Gill, 2013[27]	Prospective case series	4	Vismodegib	Clinical	5	20.0	20.0	20.0	NA	NA	NA	NA	NA	20.0	NA	NA	20.0	NA
Tang, 2016[32]	Double-blinded RCT, with placebo	1	Vismodegib	None	40	100.0	92.5	100.0	62.5	47.5	65.0	NA	NA	0	NA	NA	NA	NA
Von Hoff LoRusso[12,28]	Phase 1 trial	2	Vismodegib	Mixed	33	12.1	6.1	NA	12.1	12.1	3.0	3.0	3.0	NA	NA	3.0	6.1	NA
Simone, 2016[29]	Prospective case series	4	Vismodegib	Clinical	12	100.0	16.7	16.7	16.7	25.0	0	NA	NA	8.3	NA	NA	NA	NA
NCT01350115[33]	Phase 2 double-blinded RCT, with placebo	1	Sonidegib	Clinical	7	42.9	14.3	28.6	NA	28.6	28.6	14.3	NA	NA	28.6	14.3	NA	NA
MIKIE[31]	Phase 2 double-blinded RCT, not placebo	2	Vismodegib	NA	227	77.5	66.1	63.9	19.8	22.0	16.3	13.2	4.8	2.6	11.5	16.7	16.7	NA
RegiSONIC[30]	Prospective cohort	2	Vismodegib	Clinical	88	45.5	50.0	36.4	17.0	NA	NA	NA	NA	NA	NA	NA	NA	NA

CK, Creatine kinase; *EAS*, expanded access study; *NA*, not available or ascertainable; *RCT*, randomized clinical trial; *RECIST*, response evaluation criteria in solid tumors; *SCC*, squamous cell carcinoma; *SHHi*, sonic hedgehog inhibitor.

*Quality of evidence assessed per Oxford Centre for Evidence-based Medicine.

†Parentheses refer to the number of the premenopausal women subgroup for whom data are available.

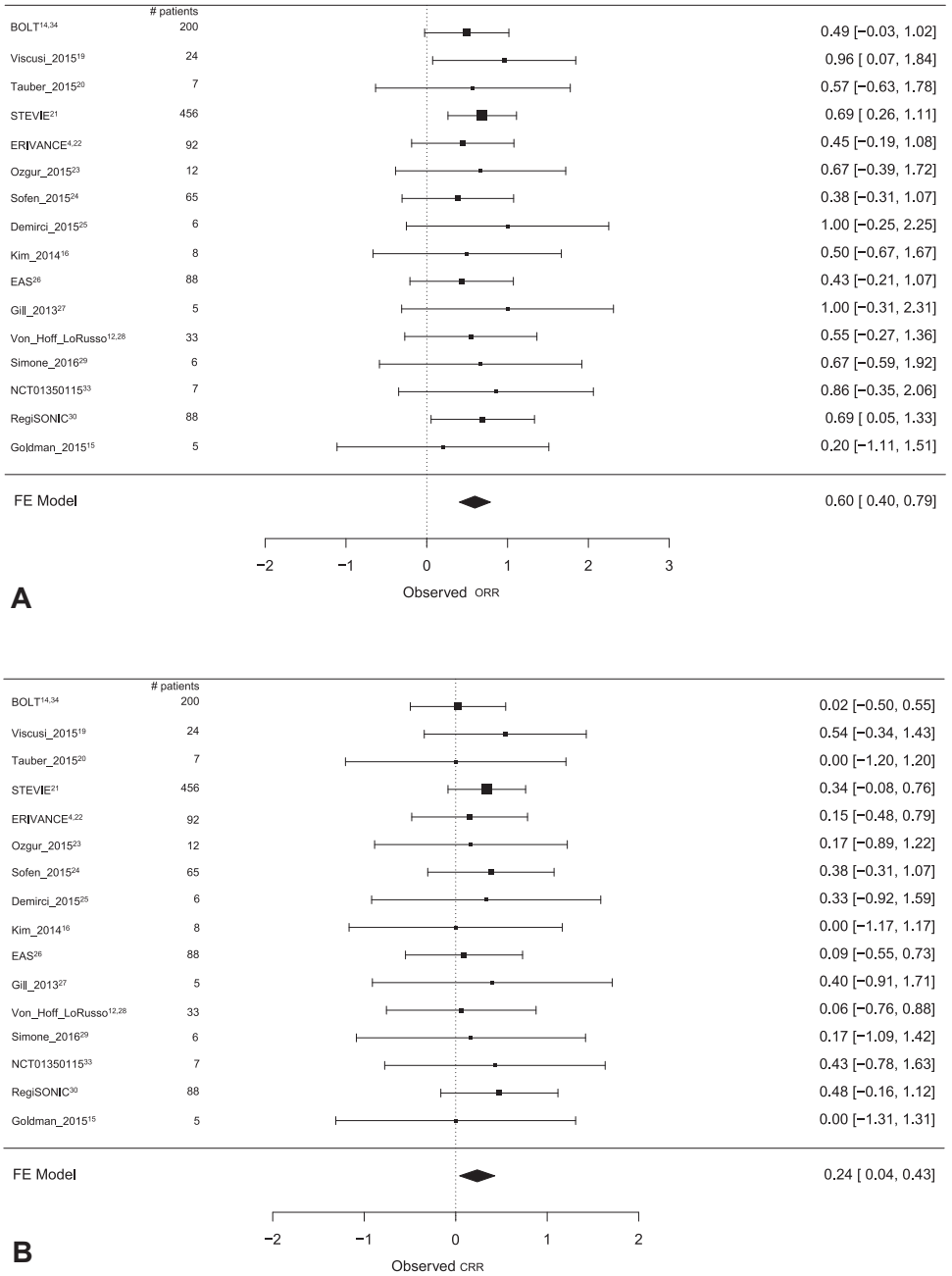


Fig 1. Forest plots of combined ORR (**A**) and CRR (**B**) using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right side. Note that the size of the black squares is related to study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *CRR*, complete response rate; *EAS*, expanded access study; *FE*, fixed effect; *ORR*, overall response rate.

bias using trim-and-fill and determined that 1 left-sided (toward null) study is lacking (funnel plot, Supplemental Fig 3; available at http://www.jaad.org). Combined ORR results were similar for vismodegib (61.9%), sonidegib (55.2%), and itraconazole (50%; limited data) and inferior for TAK-441 (20%; limited data) (Table III).

In subgroup analyses (Table III), only vismodegib and sonidegib had studies separating laBCC and mBCC. For laBCC, the ORR was 68.8% (95% CI

Table III. Efficacy of different SHHi molecules for all patients, locally advanced BCC patients, and metastatic BCC patients

Molecule	All patients			Locally advanced BCC			Metastatic BCC		
	ORR (95% CI); *P* value	CRR (95% CI); *P* value	CBR (95% CI); *P* value	ORR (95% CI); *P* value	CRR (95% CI); *P* value	CBR (95% CI); *P* value	ORR (95% CI); *P* value	CRR (95% CI); *P* value	CBR (95% CI; *P* value)
Vismodegib	61.9 (40.2 to 83.6); $<10^{-4}$	28.0 (6.3 to 49.7); .012	93.9 (70.8 to 116.9); $<10^{-4}$	68.7 (44.7 to 92.8); $<10^{-4}$	30.9 (6.9 to 55.0); .012	94.9 (69.0 to 120.9); $<10^{-4}$	39.4 (−1.9 to 80.6); .06	3.3 (−38.0 to 44.6); .88	88.8 (53.7 to 130.0); $<10^{-4}$
Sonidegib	55.2 (7.4 to 103.0); .02	8.9 (−39.0 to 56.7); .72	98.7 (50.9 to 146.6); $<10^{-4}$	56.6	3.0	98.8	14.7	0	97.1
Itraconazole	50.0	0	NA						
TAK-441	20.0	0	100.0						

The percentages for CBR, CRR, and ORR are given.
BCC, Basal cell carcinoma; *CBR*, clinical benefit rate; *CI*, confidence interval; *CRR*, complete response rate; *NA*, not available or ascertainable; *ORR*, overall response rate; *SHHi*, sonic hedgehog inhibitor.

44.7-92.8%) for vismodegib and 56.6% (95% CI not available) for sonidegib, similar but with a >10% advantage for vismodegib. In contrast, for mBCC, the ORR for vismodegib was 39.7% (95% CI −1.9% to 80.6%; P = .06), 2.7-fold higher than the ORR for sonidegib (14.7%; 95% CI not available). This intermolecular difference in ORR is statistically significant (P = .007, Fisher's exact test).

The pooled CRR (all BCC patients) was 23.5% (95% CI 4.3%-42.8%; Fig 1, *B*), indicating that a minority of SHHi-treated patients experienced a complete response (z = 2.41; P = .017). Bayesian models with random effects showed a CRR of 23.2% (95% CI 3.3%-42.5%) (Supplemental Fig 4; available at http://www.jaad.org). Some studies, particularly those assessing TAK-441 and itraconazole, had no patients with a complete response.[15,16,20] The trim-and-fill method was used to determine that no study was missing (Supplemental Fig 5; available at http://www.jaad.org). Combined CRR results were greater, and only significant, for vismodegib (28.0%; P = .012) compared with sonidegib (8.9%; P = .72).

In subgroup analyses for laBCC, the CRR was 30.9% (95% CI 6.9-55.0%; P = .012) for vismodegib, meaning that many of these patients could expect cure. In contrast, only a minority of laBCC patients achieved cure with sonidegib (3.0%, 95% CI not available). This intermolecule difference in CRR is statistically significant (P < .0001, Fisher's exact test). For mBCC, both molecules did not lead to complete responses (range 0%-3.3%).

At least 132 patients across all studies had Gorlin-Goltz syndrome. However, in most studies, efficacy results are not available or stratified on the basis of Gorlin-Goltz status. As such, only 14 affected patients can be evaluated for efficacy, with point estimates of 78.6% for ORR and 35.7% for CRR. Of these, 7 patients were taking sonidegib (ORR 85.7%, CRR 42.7%), and 7 were taking vismodegib (ORR 71.4%, CRR 28.6%). Thus, data are lacking to determine whether differences exist in efficacy related to patients' Gorlin-Goltz syndrome status.

Finally, we computed CBRs, an oncologic outcome defined as the percentage of patients given a certain treatment who have at least stable disease (ie, percentage of patients with stable disease plus patients who responded). Pooled CBR estimate was 94.9% (95% CI 74.4%-115.4%; Supplemental Fig 6; available at http://www.jaad.org). CBR results were similar for all 4 molecules. As expected, the CBR was greater for laBCC patients than mBCC patients.

Safety of SHHis

The 16 studies in Table II were pooled by using fixed-effects linear models to determine the

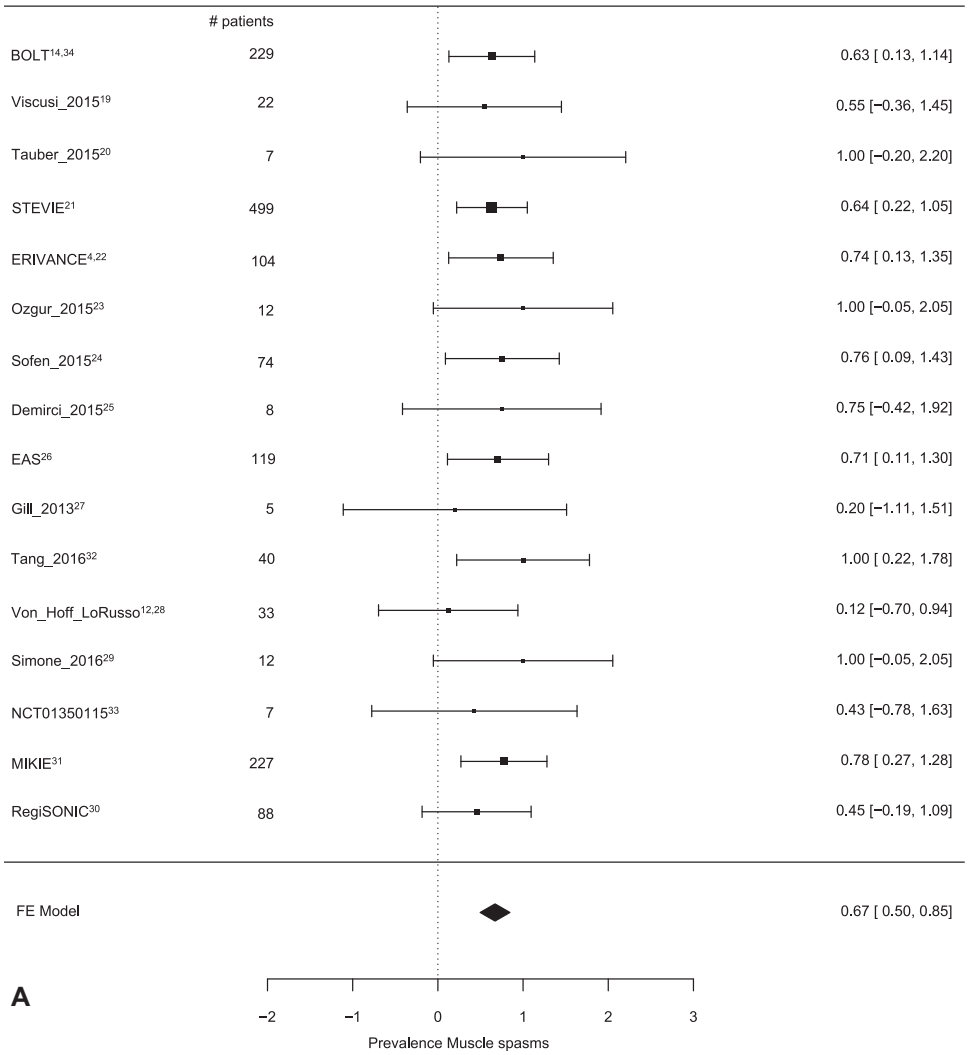
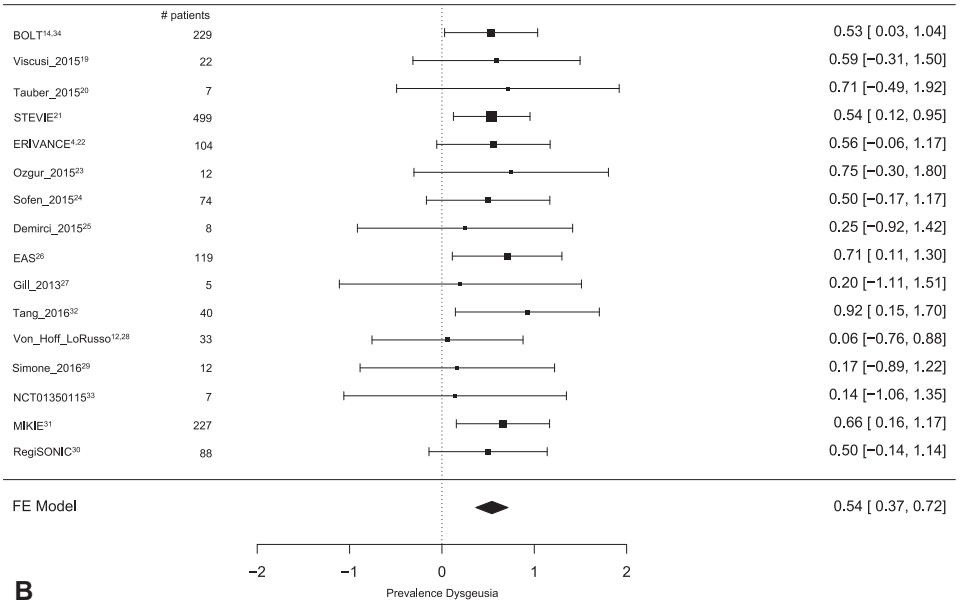


Fig 2. Forest plots of combined muscle spasms prevalence (**A**), dysgeusia prevalence (**B**), and alopecia prevalence (**C**) using linear models with FEs. Study name and number of patients in each study are given on the left side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% confidence interval are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect.

prevalence of frequent side effects.[4,12,14,19-34] For itraconazole, only 2 side effects were reported: fatigue and heart failure, both occurring in 1 out of 19 patients.[16] For TAK-441, side effects in the study concerned BCC and non-BCC malignancies and, thus, were excluded from pooled prevalences.[15] For intermolecule comparisons, an absolute difference >10% was considered clinically important. The 3 most common side effects were muscle spasms, dysgeusia, and alopecia. The pooled prevalence of muscle spasms was 67.1% (95% CI 49.6%-84.6%; Fig 2, *A*), dysgeusia 54.1% (95% CI 36.6%-71.6%; Fig 2, *B*), and alopecia 57.7% (95% CI 39.8%-75.5%; Fig 2, *C*). Dysgeusia occurred at similar rates for vismodegib, sonidegib, and TAK-441 (Table IV). Muscle spasms and alopecia were equally prevalent for vismodegib (68.2% and 58.9%, respectively) and sonidegib (60.3% and 50.7%, respectively) and less so for TAK-441 (44% and 26%, respectively). Bayesian models with random effects showed similar



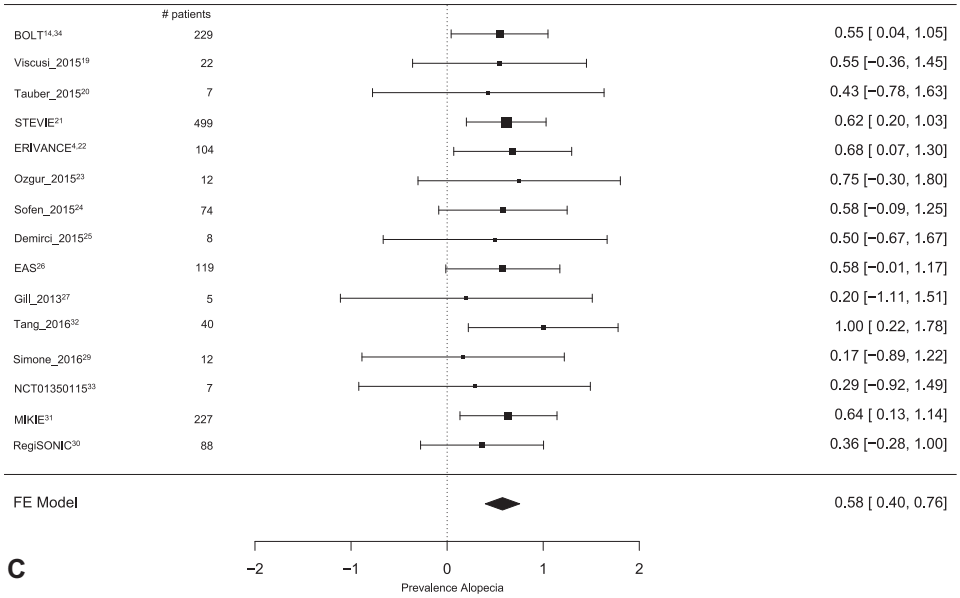


Fig 2. (*continued*).

results. The 3 side effects, therefore, could be expected in most patients ($P < .0001$). Other side effects occurring significantly more often than expected by chance alone included weight loss (32.2%, 95% CI 13.2%-51.2%; $P < .0001$), fatigue (25.9%, 95% CI 7.1%-44.7%; $P = .007$), and nausea (24.2%, 95% CI 5.0%-43.5%; $P = .013$) (Supplemental Figs 7-9; available at http://www.jaad.org). Fatigue was less prevalent for itraconazole (1/19 patients), more prevalent for TAK-441 (47%), and intermediate for vismodegib (24.5%) and sonidegib (32.9%). Nausea was nearly twice more likely for sonidegib (39.2%) than vismodegib (21.2%), and weight loss occurred in similar proportions (31.3% vismodegib; 37.6% sonidegib). Other side effects (not statistically different among molecules) are presented in Supplemental Figs 10-16 (available at http://www.jaad.org). Among these side effects, myalgias and vomiting were ~2X and ~6X, respectively, more likely to occur in patients receiving sonidegib (myalgias 22.2%; vomiting 20.5%) than vismodegib (myalgias 9.6%; vomiting 3.7%).

Table IV. Prevalence of major side effects for different SHHi molecules

Side effects	Vismodegib, % (95% CI); *P* value	Sonidegib, % (95% CI); *P* value	Itraconazole, %	TAK-441,* %
Muscle spasms	68.2 (49.4 to 87.1); $<10^{-4}$	60.3 (13.8 to 106.8); .011	NA	**44.0**
Dysgeusia	55.2 (36.3 to 74.1); $<10^{-4}$	47.5 (1.0 to 94.0); .045	NA	47.0
Alopecia	58.9 (39.5 to 78.3); $<10^{-4}$	50.7 (4.2 to 97.2); .033	NA	**26.0**
Weight loss	31.3 (10.9 to 51.8); .003	37.6	NA	**15.0**
Fatigue	24.5 (4.0 to 45.1); .019	32.9 (−13.6 to 79.4); .17	**5.3**	**47.0**
Nausea	21.2 (0.1 to 42.3); .49	**39.2** (−7.3 to 85.6); .10	NA	**47.0**
Myalgias	9.6 (−19.1 to 38.3); .51	**22.2** (−24.3 to 68.7); .35	NA	NA
Vomiting	3.7 (−36.1 to 43.5); .85	**20.5**	NA	**24.0**
Skin SCC	4.0 (−20.0 to 27.0); .77	NA	NA	NA
Increased CK	11.5	13.5 (−32.9 to 60.0); .57	NA	NA
Diarrhea	17.1 (−4.9 to 39.1); .13	23.7 (−22.3 to 70.2); .32	NA	24.0
Decreased appetite	21.0 (−2.9 to 44.8); .08	28.8	NA	26.0
Amenorrhea	35.0 (−25.0 to 95.0); .26	NA	NA	NA

Bolded are side effects with an absolute difference in prevalence ± 10% compared with vismodegib.
BCC, Basal cell carcinoma; *CI*, confidence interval; *CK*, creatine kinase; *NA*, not available or ascertainable; *SCC*, squamous cell carcinoma; *SHHi*, sonic hedgehog inhibitor.
*Includes BCC and non-BCC patients.

Amenorrhea was only reported in 3 studies,[21,22,26] including 43 reproductive age women. The pooled prevalence was 34.9% (95% CI −25.2% to 94.9%; Supplemental Fig 17; available at http://www.jaad.org). Despite all studies being positive, pooled data did not achieve statistical significance ($P = .26$), likely due to the small sample size. Of note, amenorrhea and SCC diagnosis were only evaluated for vismodegib.

DISCUSSION

Our meta-analysis reveals that clinicians should expect partial responses in laBCC with vismodegib or sonidegib treatment. Compared with sonidegib, vismodegib had a higher ORR and CRR for laBCC and higher ORR for mBCC. Moreover, sonidegib caused more upper gastrointestinal disturbances and myalgias than vismodegib. These findings favor the use of vismodegib over sonidegib in clinical practice. One small study reported that sequential therapy with sonidegib for vismodegib-resistant BCC is ineffective.[35] Evidence showed resistance to both agents involves similar mechanisms.[36] For itraconazole and TAK-441, there are limited data to draw conclusions. Contrasting with vismodegib and sonidegib, the side effects of itraconazole use are mild, except for the well-known risk for heart failure seen in a few patients identified in previous studies involving the use of itraconazole as an antifungal agent.[37]

Common side effects of SHHi therapy tend to incapacitate patients, leading to high discontinuation rates. Over 25% of patients stopped treatment due to side effects.[13] Most side effects are reversible after therapy cessation,[38] except some cases of persistent alopecia have been reported.[39] Patients should be warned before therapy of pertinent side effects to encourage compliance. Algorithms exist for SHHi side effect management.[40] Of note, sonidegib exposure and maximum concentration are greater in East Asian populations and might warrant lower doses[41]; this finding has not been reported for vismodegib.

There are several limitations to performing this meta-analysis to assess the efficacy of SHHi molecules. First, most patients came from 2 studies: STEVIE[21] and BOLT.[34] Second, variances were not provided in most studies, so values were estimated from sample sizes. Third, nearly all studies lacked placebo, and there was insufficient data to determine progression-free survival. Fourth, evaluation of treatment outcomes remained heterogeneous (from clinical outcome to histopathologic clearance); most studies used objective criteria like RECIST.

A new diagnosis of SCC was made in 3.6% of patients taking vismodegib, which was not statistically significant in our analysis ($P = .77$). The estimate was smaller in larger studies. For example, in STEVIE,[21] SCC developed in 0.8% of 499 patients. SCC usually develops within 1 year of starting vismodegib.[42,43] In a case−control study, exposure to vismodegib was significantly associated with an ~8-fold increased risk for SCC, after adjusting for age and Gorlin-Goltz syndrome status.[44] Confounding factors for finding SCC in BCC patients include shared risk factors and careful skin examination after cancer diagnosis. In comparison, the risk for SCC

after melanoma treatment with BRAF inhibitor monotherapy is higher (12%-27%) and presents quicker (mean time from exposure to diagnosis of 7 weeks).[45,46]

Studies are currently underpowered to determine whether amenorrhea is a significant side effect. It is unclear whether amenorrhea was asked systematically in all reproductive age women or whether there was self-reporting bias. Amenorrhea is important in 2 groups of young women, those suffering from Gorlin-Goltz syndrome and those with increased ultraviolet light exposure. If the increased incidence of BCC in women <40 years of age persists,[47] amenorrhea should be assessed systematically.

The finding that itraconazole induced a partial response or disease stability in some patients with BCC[16] warrants larger clinical trials with longer follow-up to evaluate efficacy and side effects, especially heart and liver failure.[16] New SMO inhibitors are under development, while GLI inhibitors, targeting the downstream GLI family of transcription factors, might yield different efficacy and safety profiles than SMO inhibitors.[11]

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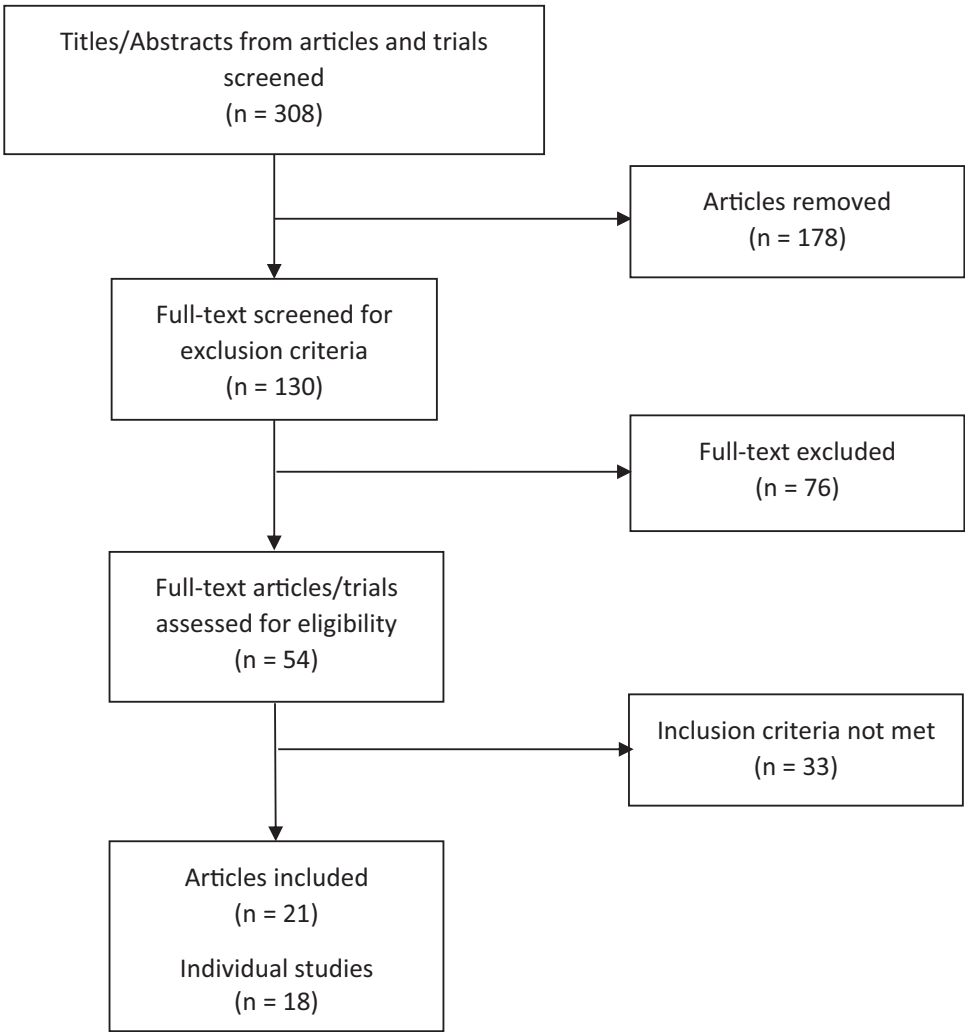
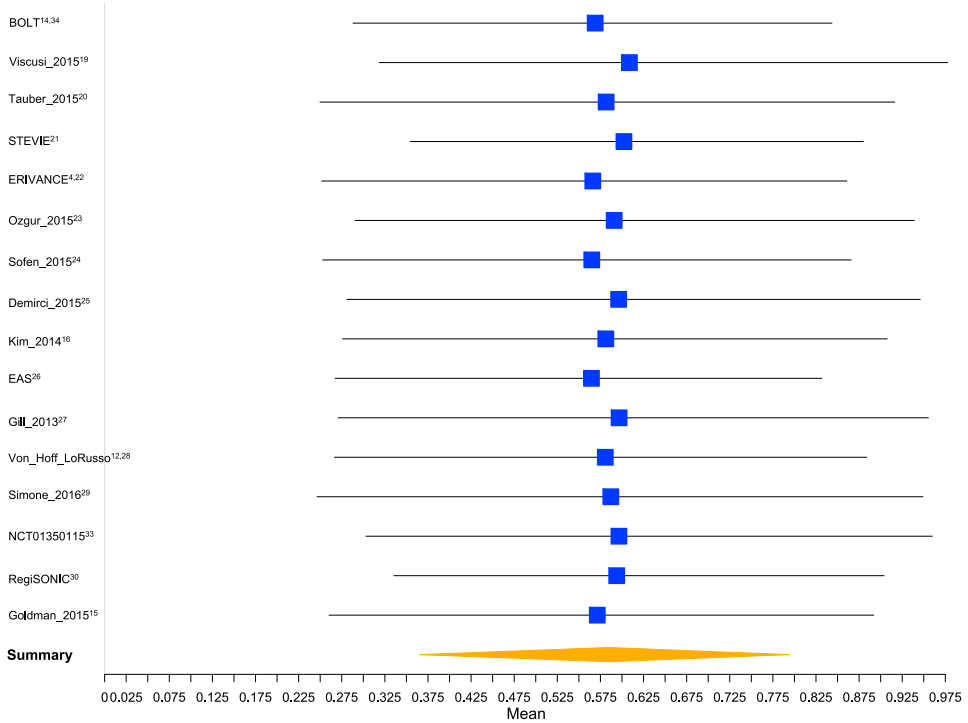
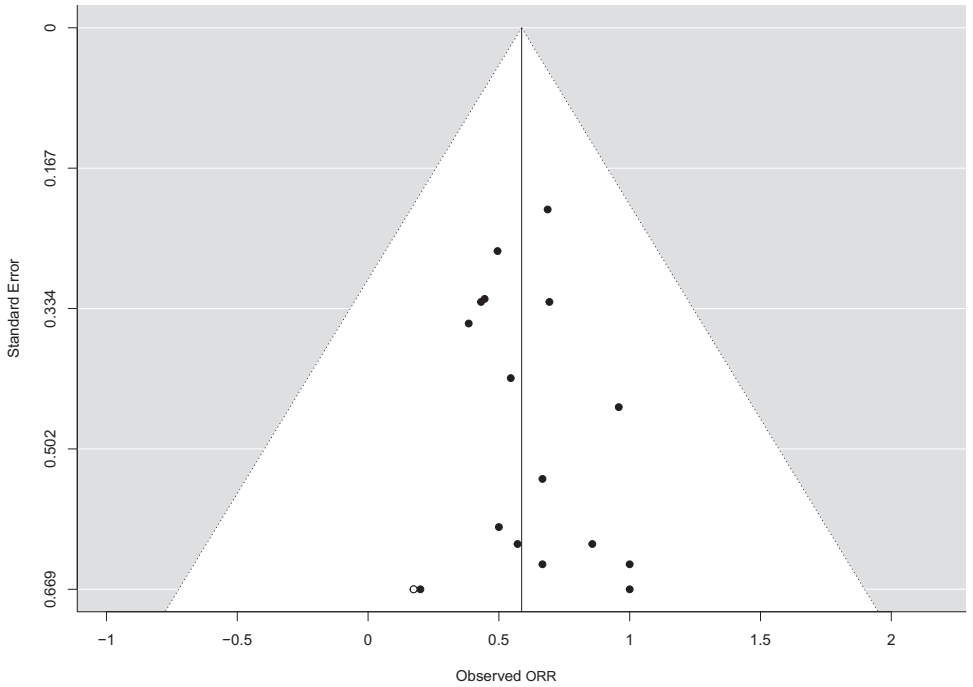


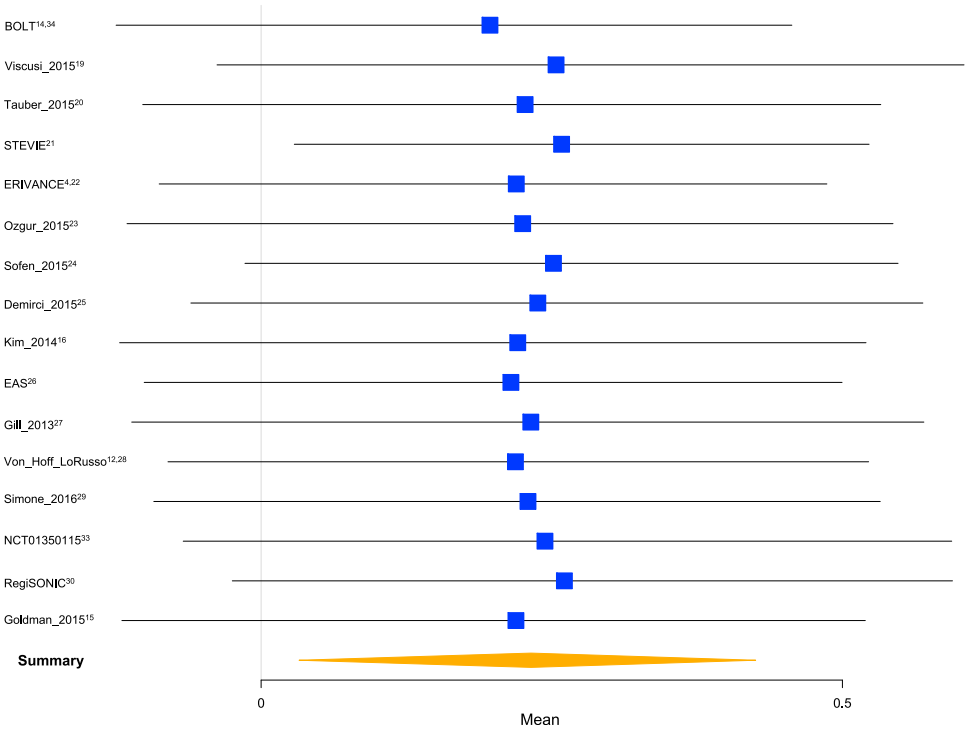
Supplemental Fig 1. PRISMA flow diagram. *PRISMA*, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.



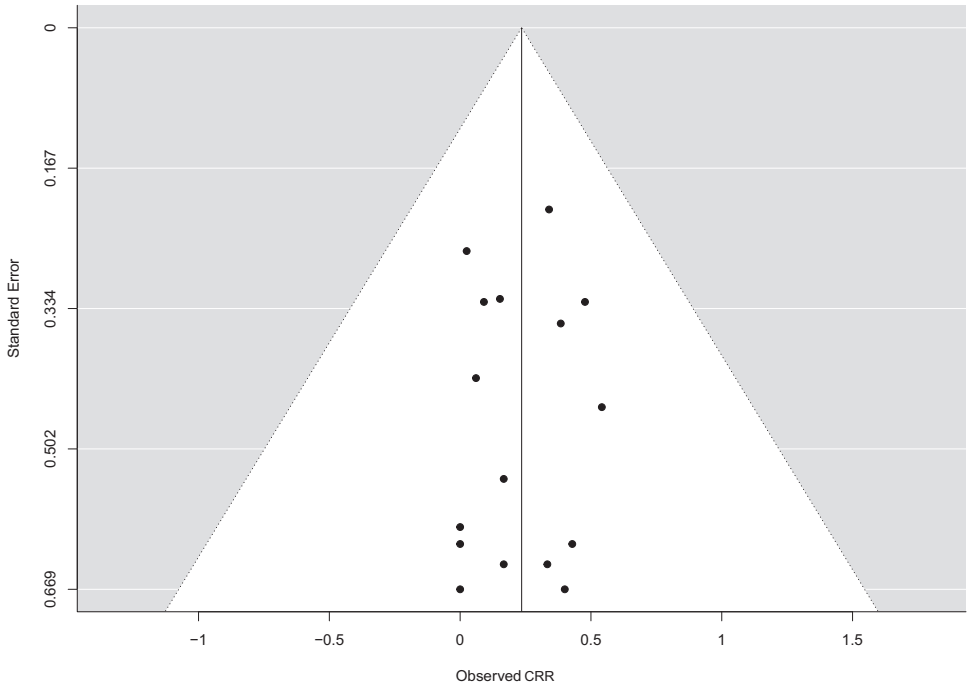
Supplemental Fig 2. Forest plot of combined overall response rate (ORR) for Bayesian models with random effects. Study name and number of patients in each study are given on the left-hand side. Bayesian estimates for individual studies are represented by blue squares, along with 95% confidence intervals. Note that the size of the blue squares is unrelated to study contribution to final estimates. The pooled estimate and 95% confidence interval are represented by the orange diamond. *EAS*, Expanded access study.



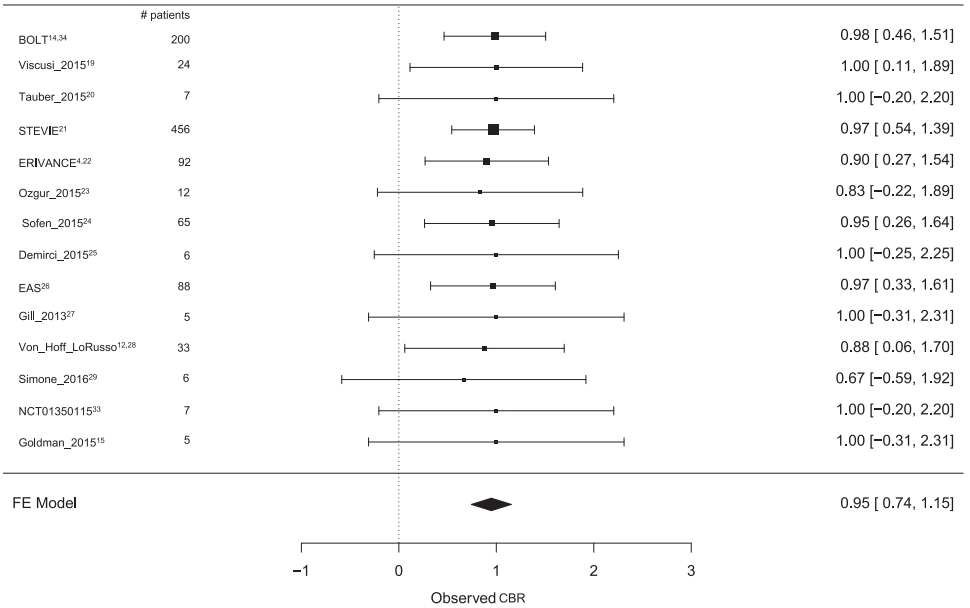
Supplemental Fig 3. Funnel plot for combined ORR. Filled black circles indicate actual studies included in the meta-analysis. Open, unfilled circles indicate where missing studies would lie to account for publication bias. The *x*-axis indicates ORRs estimated from individual studies. The *y*-axis indicates precision of individual studies, showing the standard error. The vertical plain line indicates the pooled ORR from the meta-analysis using linear models with fixed effects. Dotted lines indicate the boundary of a pseudo-confidence interval for the funnel plot. *ORR*, Overall response rate.



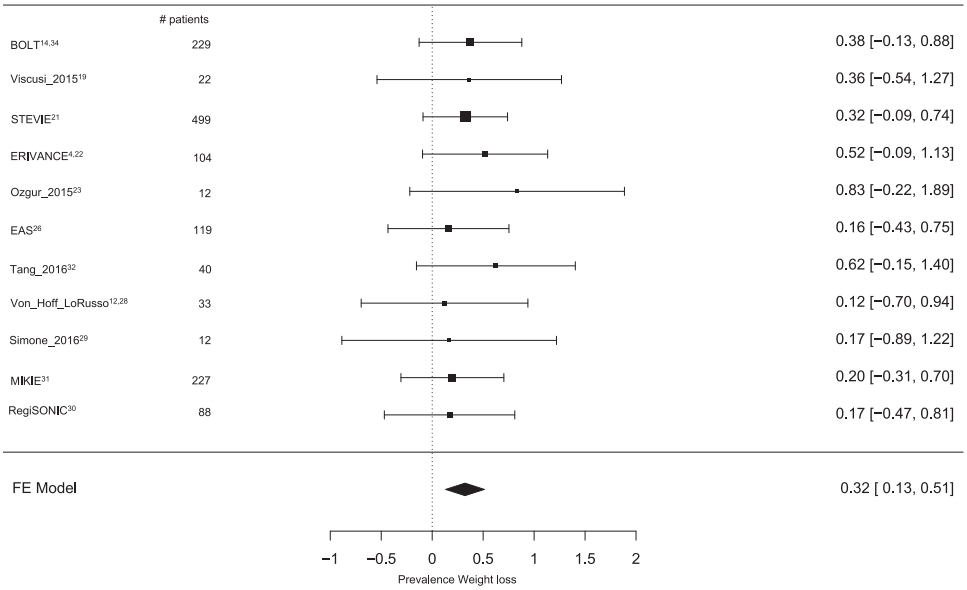
Supplemental Fig 4. Forest plot of combined complete response rate (CRR) for Bayesian models with random effects. Study name and number of patients in each study are given on the left-hand side. Bayesian estimates for individual studies are represented by blue squares, along with 95% confidence intervals. Note that the size of the blue squares is unrelated to study contribution to final estimates. The pooled estimate and 95% confidence interval are represented by the orange diamond. *EAS*, Expanded access study.



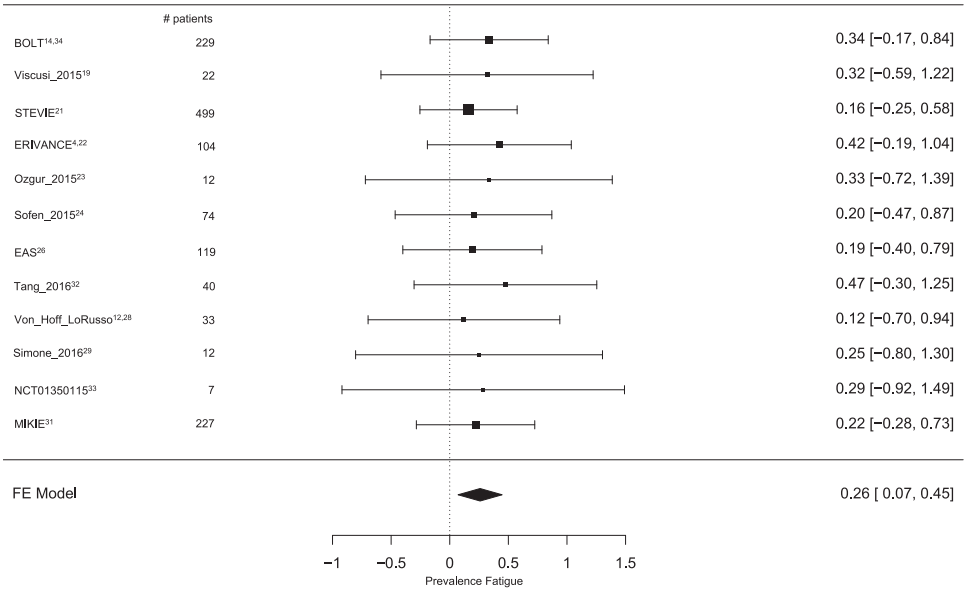
Supplemental Fig 5. Funnel plot for combined CRR. Filled black circles indicate actual studies included in the meta-analysis. The *x*-axis indicates CRR estimated from individual studies. The *y*-axis indicates precision of individual studies, showing the standard error. The vertical plain line indicates the pooled CRR from our meta-analysis using linear models with fixed effects. Dotted lines indicate the boundary of a pseudo-confidence interval for the funnel plot. *CRR*, Complete response rate.



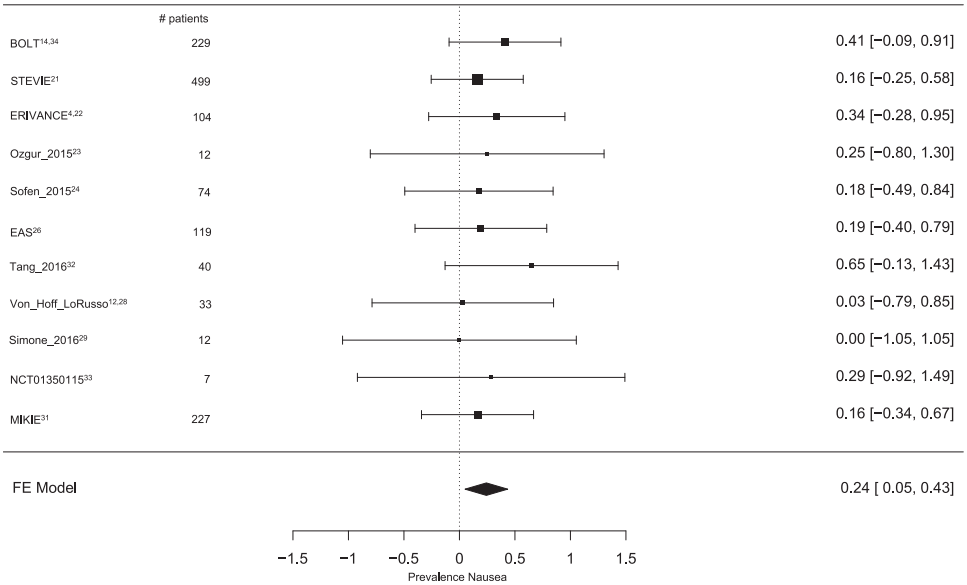
Supplemental Fig 6. Forest plot of the combined CBR using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with the 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CBR*, Clinical benefit rate; *CI*, confidence interval; *EAS*, expanded access study; *FE*, fixed effect.



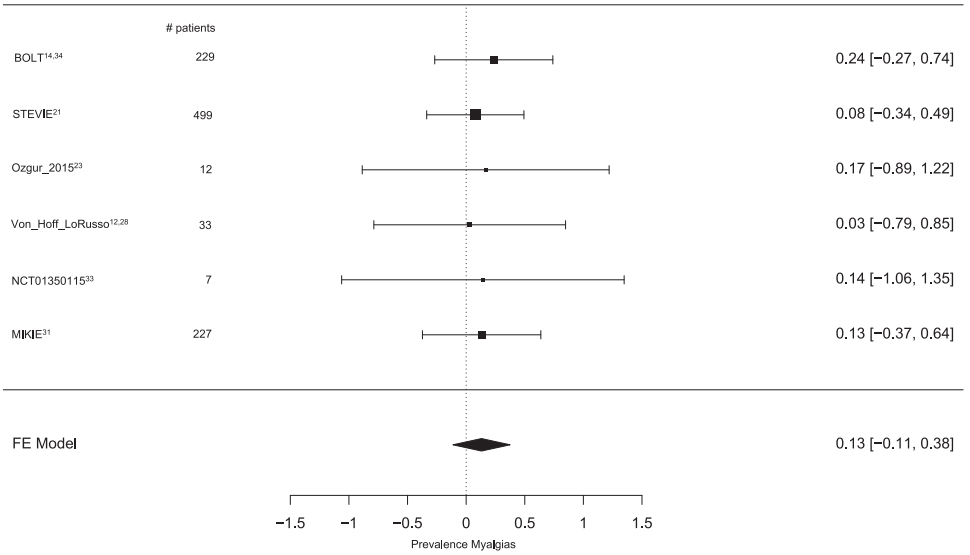
Supplemental Fig 7. Forest plot of combined weight loss prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect.



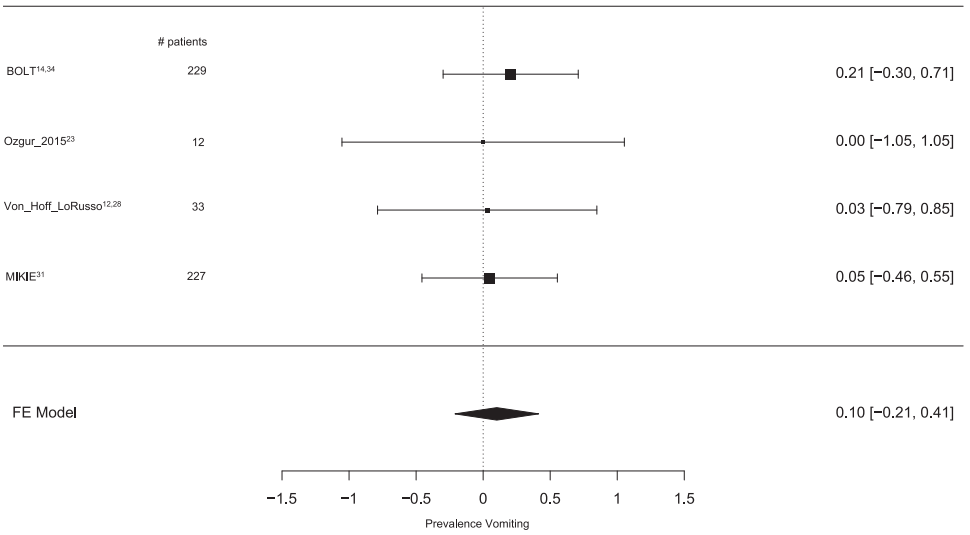
Supplemental Fig 8. Forest plot of combined fatigue prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from their sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect.



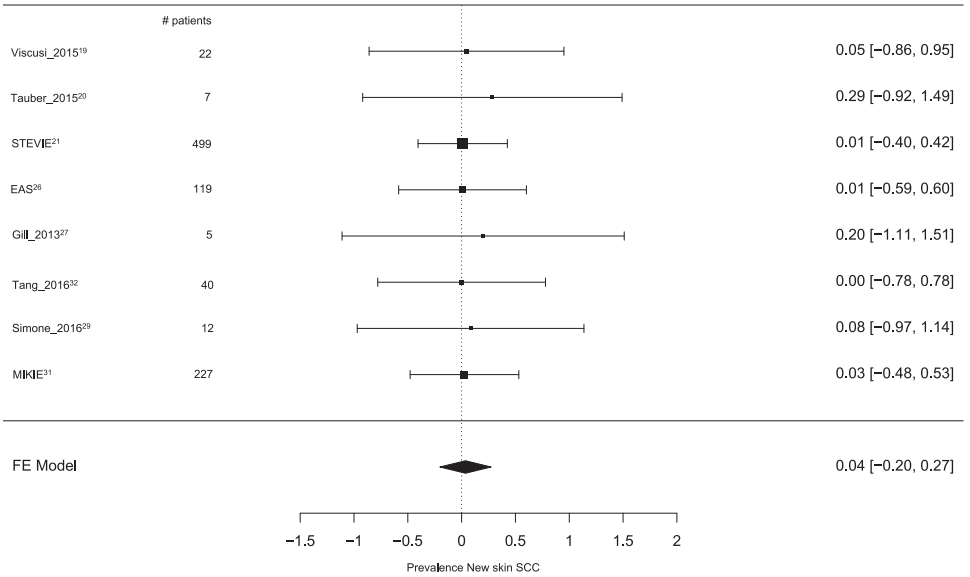
Supplemental Fig 9. Forest plot of the combined nausea prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect.



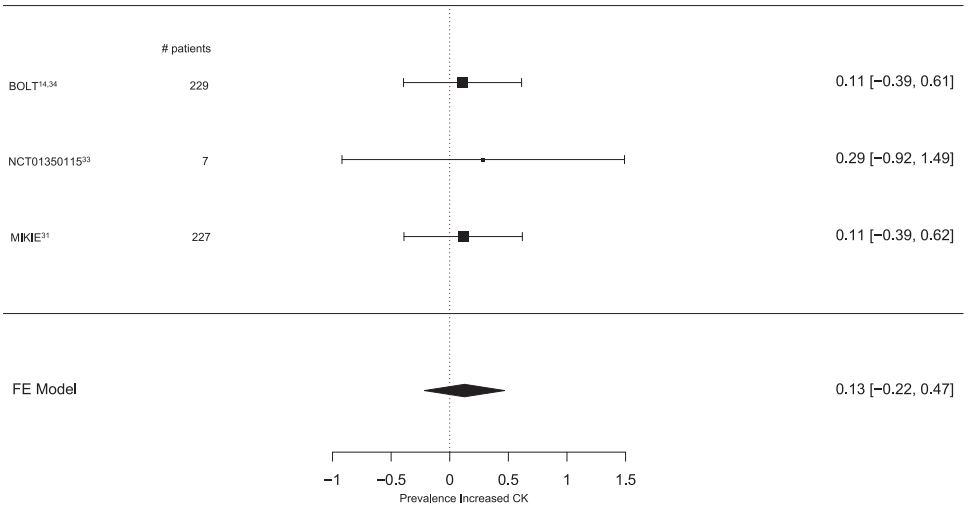
Supplemental Fig 10. Forest plot of the combined myalgia prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *FE*, fixed effect.



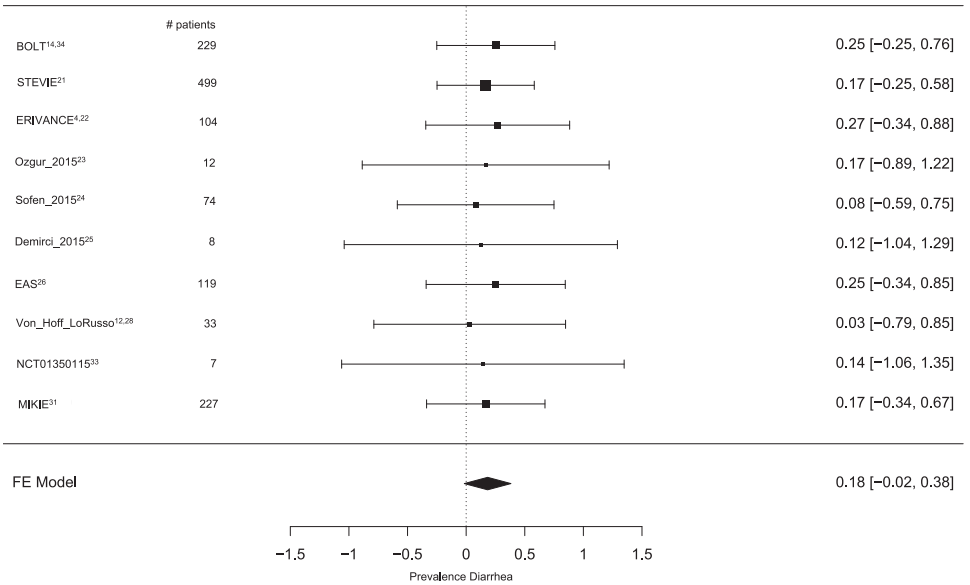
Supplemental Fig 11. Forest plot of combined vomiting prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *FE*, fixed effect.



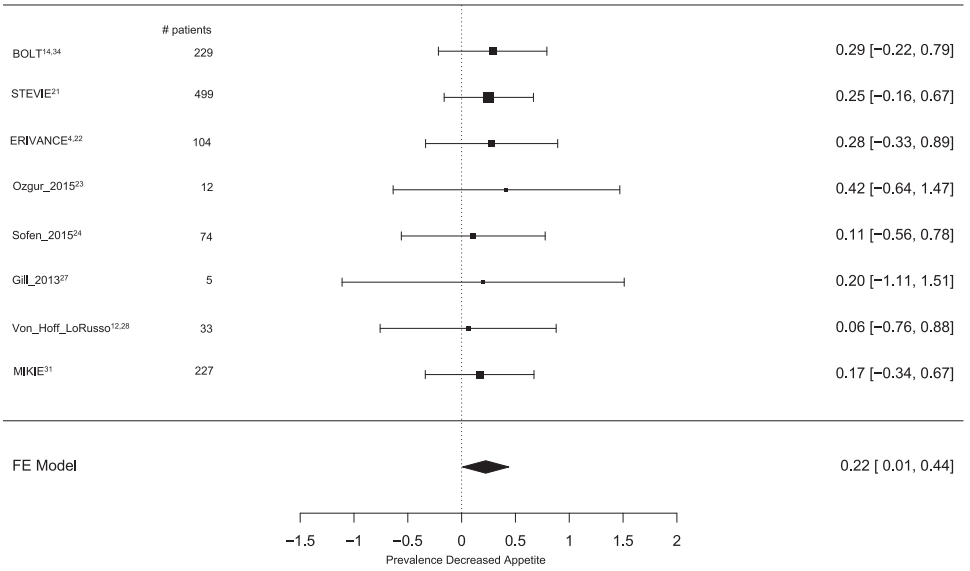
Supplemental Fig 12. Forest plot of combined new diagnosis of skin SCC prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect; SCC, squamous cell carcinoma.



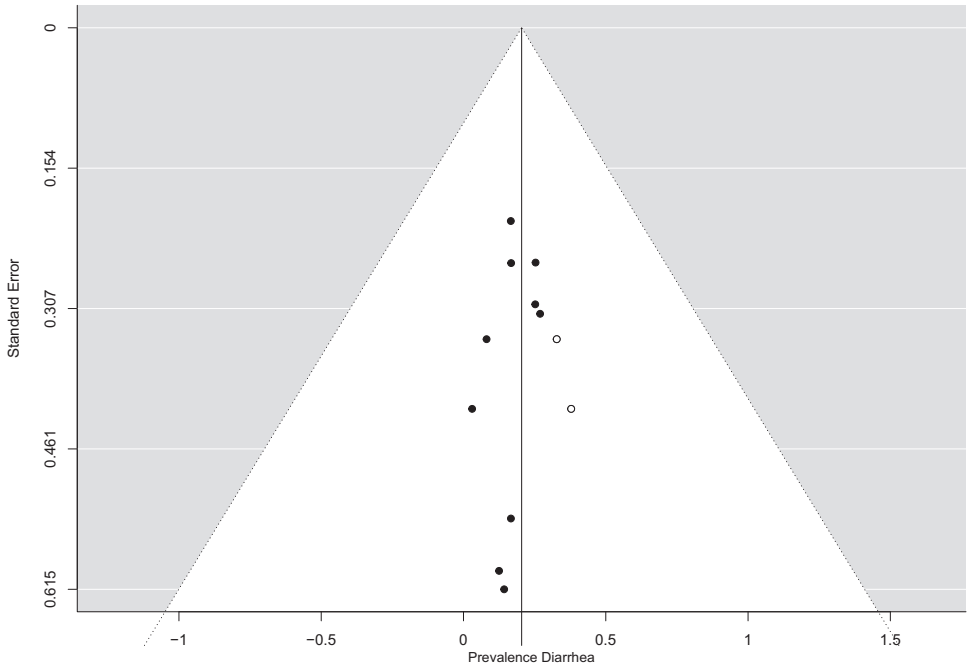
Supplemental Fig 13. Forest plot of combined increased creatine kinase prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *FE*, fixed effect.



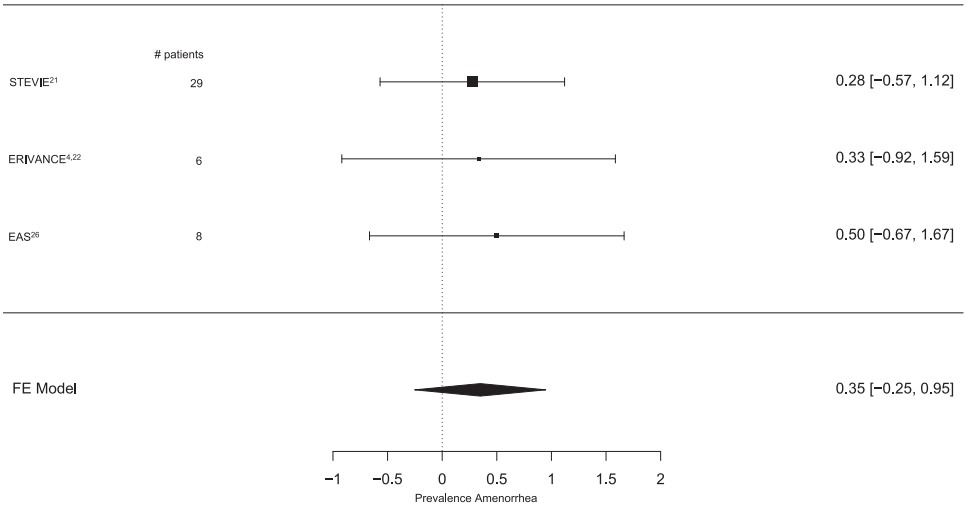
Supplemental Fig 14. Forest plot of combined diarrhea prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect.



Supplemental Fig 15. Forest plot of combined decreased appetite prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *FE*, fixed effect.



Supplemental Fig 16. Funnel plot for combined diarrhea prevalence. Filled black circles indicate the actual studies included in the meta-analysis. Open, unfilled circles indicate where missing studies would lie to account for publication bias. The *x*-axis indicates diarrhea prevalence estimated from individual studies. The *y*-axis indicates precision of individual studies, showing the standard error. The vertical plain line indicates the pooled prevalence from meta-analysis using linear models with fixed effects. Dotted lines indicate the boundary of a pseudo-confidence interval for the funnel plot.



Supplemental Fig 17. Forest plot of combined amenorrhea prevalence using linear models with FEs. Study name and number of patients in each study are given on the left-hand side. Estimates for individual studies are represented by black squares, along with their 95% CIs; numerical values are appended to the right-hand side. Note that the size of the black squares is related to the study contribution estimated from sample sizes. The pooled estimate and 95% CI are represented by the black diamond at the bottom center of the graph; numerical values are found at the bottom right corner. *CI*, Confidence interval; *EAS*, expanded access study; *FE*, fixed effect.