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# Research article

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# A real-world disproportionality analysis of FDA adverse event reporting system (FAERS) events for alpelisib

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# ABSTRACT

In this study, we delved into the safety profile of alpelisib, an FDA-approved treatment for hormone receptor-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer, and PIK3CA-Related Overgrowth Spectrum (PROS). Despite its approval, real-world, long-term safety data is lacking. Our research scrutinizes the FDA database to assess alpelisib 's safety. We retrospectively analyzed data from April 2019 to June 2023 using four algorithms. Among 7,609,450 reports, 6692 implicated alpelisib as the primary suspected drug, uncovering adverse events (AEs) across 26 organ systems. Notably, we identified 21 previously unlisted AEs. Furthermore, differences in AEs emerged between patients with PIK3CA-mutated breast cancer and those with PROS. This study provides vital insights for healthcare professionals to navigate AEs in clinical practice and informs future research for enhancing alpelisib 's safety profile.

### 1. Introduction

Alpelisib, a highly selective  $\alpha$ -specific inhibitor of phosphatidylinositol 3-kinases (PI3K), shows a remarkable 50-fold preference for inhibiting the p110 $\alpha$  isoform over others [1]. This specificity is particularly relevant given that mutations in the PIK3CA gene drive PI3K-p110 $\alpha$  activation, and Alpelisib emerges as an effective treatment for conditions linked to PIK3CA mutations [2,3]. Its Food and Drug Administration (FDA) approval in May 2019 was a pivotal moment, introducing it as the first treatment for hormone receptor (HR)-positive, HER2-negative, PIK3CA-mutated advanced or metastatic breast cancer and PIK3CA-Related Overgrowth Spectrum (PROS) [4,5]. Clinical practice has since validated alpelisib's efficacy and safety, solidifying its role in treatment strategies [6–8].

The widespread use of alpelisib after FDA approval has brought attention to its real-world adverse events (AEs). The FDA's prescribing information lists common AEs such as changes in glucose and creatinine levels, diarrhea, rash, lymphocyte count reductions, and more. Subsequent safety trials have underscored these AEs, advocating for early detection and intervention strategies, including dose adjustments, to mitigate toxicity [9]. However, patient responses can vary widely due to unique health conditions and other

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The limitations of clinical trials, such as small sample sizes and short observation periods, highlight the need for extensive postmarketing safety research in real-world settings [10]. Data from these settings are crucial for understanding the safety profile of alpelisib across diverse patient populations. Despite this, there is a notable lack of comprehensive studies focusing on alpelisib's real-world AEs.

Alpelisib is FDA-approved for two distinct conditions, PROS and PIK3CA-mutated breast cancer. These conditions differ in epidemiology and clinical presentation, and so does the prescribed alpelisib dosage for each [11]. Therefore, the AEs can vary significantly based on the indication, making it essential to study AEs in real-world contexts for each indication.

The FDA Adverse Event Reporting System (FAERS) is a key public database for post-marketing drug safety monitoring [12]. In recent years, more and more drug safety profile studies based on FAERS have been published, which shown that validity of the database and data obtained by FAERS has been recognized. Through comprehensive evaluation and scrutiny, our study investigated the disproportionality of reported AEs linked with alpelisib. This analysis revealed AEs that might have been undetected prior to FDA approval. Such data is invaluable for guiding careful alpelisib use in clinical settings and spurring further, more comprehensive research.

# 2. Methods

The FAERS database operates as a pivotal Spontaneous Reporting System (SRS), methodically aggregating global reports of AEs to fortify the FDA's post-market surveillance endeavors subsequent to the introduction of drugs and biotherapy products [13]. This system assumes a critical role in discerning and evaluating potential signals, concurrently quantifying the associations between particular drugs and the AEs documented by individuals. The database undergoes quarterly updates, encompassing an extensive spectrum of AE accounts, documentation of medication mishaps, and instances of product quality grievances.

# 2.1. Data sources and procedures

In this study, our primary focus was on extracting and scrutinizing pertinent reports related to alpelisib from the FAERS database, available at https://fis.fda.gov/extensions/FPD-QDE-FAERS/FPD-QDE-FAERS.html. The FAERS data package is presented as a zipped package on the website. The data file has seven sections containing demographic and management information, drug information, AEs, patient outcomes, reporting sources, starting and ending dates of treatment with reported drugs, indications, and deleted cases. We compiled data from the drug's initial FDA approval in the second quarter of 2019 up to the latest available data in the second quarter of 2023. However, given the potential for duplicated entries in the FAERS database, a thorough deduplication process was undertaken.

AEs recorded in the FAERS database underwent a comprehensive coding process using the Medical Dictionary for Regulatory Activities 26.0 (MedDRA 26.0). To effectively categorize these events, the hierarchical structure of the MedDRA terminology was strategically organized into five distinct levels: system organ class (SOC), high-level group term (HLGT), high-level term (HLT), preferred term (PT), and lowest-level term (LLT). Our specific focus within this study was to capture all AEs associated with alpelisib, a specific drug, as outlined in the REAC files meticulously curated within the FAERS database. This approach enabled us to systematically identify and isolate these events, subsequently allowing for a detailed analysis of their frequency and severity. This analysis was conducted using MedDRA classifications, both at the broader SOC level and the more detailed PT level.

In the context of characterizing AEs within drug-related reports, the responsibility of assigning these codes lies with the individuals reporting the events. The potential codes available for assignment were: 1 =suspect, 2 = concomitant, and 3 = interacting. In order to enhance the precision and accuracy of our analysis, we opted to designate the code "1" as "PS" (primary suspected) within the DRUG files. This strategic decision was made to elevate the accuracy of our analysis and overall conclusions.

#### 2.2. Statistical analysis

Disproportionality analysis is a crucial technique in pharmacovigilance studies, playing a vital role in identifying potential signals indicating AEs associated with a drug [14]. This methodology involves a comparative assessment of the frequency of AEs linked to a specific drug against the occurrence of AEs related to all other medications. Fundamentally, it relies on the concept that a signal emerges during data extraction when the incidence rate of a particular AE for a given drug significantly surpasses the background occurrence rate observed across the entire database. This deviation from the norm must exceed a predetermined threshold or set of criteria to be considered statistically significant.

In our analysis, we employed both Frequentist and Bayesian methodologies in the framework of disproportionality analysis. This dual approach enabled us to explore the intricate relationship between a drug and a specific AE. This exploration was facilitated through the application of several essential metrics, including the reporting odds ratio (ROR), the proportional reporting ratio (PRR), the Bayesian confidence propagation neural network (BCPNN), and the multi-item gamma Poisson shrinker (MGPS) [15]. In our study, the identification of AE signals required meeting the criteria stipulated by all four algorithms simultaneously. For a detailed understanding of the mathematical equations and criteria governing each of these algorithms, we refer readers to Supplementary Table S1. All measures of disproportionality are based on the same principles of calculation using the 2 × 2 table, as presented in Supplementary Table S2.

In our study, stratified analysis was also employed as a key methodological approach. This process entailed dividing the dataset into distinct subsets based on predefined criteria such as indications, gender, age, and the concurrent use of medications. We then

conducted separate analyses within each subset. This allowed for an in-depth examination of patterns and variations specific to each group, facilitating a comprehensive understanding of the data that might be obscured in a broader analysis.

# 3. Results

#### 3.1. Characteristics of AE reports

Throughout the course of the study, a total of 7,609,450 AE reports were initially scrutinized. Following a meticulous elimination of duplicate entries, a refined dataset of 6692 reports directly associated with alpelisib remained, as depicted in Fig. 1.

To shed light on the essential traits of patients experiencing AEs specifically linked to alpelisib, a concise compilation of their fundamental characteristics was meticulously presented in Table 1. Apart from a reported number of 899 in the first and second quarters of 2023, the largest number of AE reports reached 1752 in the year 2022. This was closely followed by the year 2021, recording 1686. Of the patients who experienced AEs associated with alpelisib collected from FAERS, AEs occurred mainly in female (n = 5814, 95.64%), adult (n = 2,367, 96.86%) and breast cancer emerges as the predominant indicated condition (n = 2,971, 81.53%). Among the serious outcomes documented, hospitalization stood at the forefront (n = 1,225, 34.80%), followed by cases culminating in fatality (n = 945, 26.85%). Our exploration of the top five combination drugs associated with alpelisib-related AEs led us to identify fulvestrant, metformin, faslodex, letrozole, and ribociclib as the primary contenders in this regard.

# 3.2. Disproportionality analysis

The signal reports for alpelisib at the SOC level are presented in Table 2. AE occurrences linked to alpelisib encompass a wide spectrum of 26 distinct organ systems. Among these, "General disorders and administration site conditions (SOC: 10018065, n = 2770)", "Gastrointestinal disorders (SOC: 10017947, n = 2263)" and "Metabolism and nutrition disorders (SOC: 10027433, n = 2053)" emerged more reported number. The latter two exhibited a positive signal detection through the ROR, Information Component (IC),



Fig. 1. The flow diagram of selecting alpelisib-related AEs from FAERS database DEMO: demographic file DRUG: drug file REAC: reaction file PS: primary suspect

# Y. Lin et al.

#### Table 1

Clinical characteristics of reports with alpelisib from the FAERS database (April 2019 to June 2023).

Characteristics	Alpelisib-induced AE reports ( $n = 6692$ )				
Number of events	Available number	Case number	Case proportion		
Gender, n (%)	6079	-	90.84%		
Female	-	5814	95.64%		
Male	-	265	4.36%		
Age (years), n (%)	2392	_	35.74%		
<18	-	75	3.14%		
$18 \leq and \leq 65$	-	1277	53.39%		
>65	-	1090	45.57%		
Median (IQR)	-	63 (54–71)	_		
Weight (Kg), n (%)	877	_	13.11%		
<80	_	686	78.22%		
$80 \le and \le 100$	-	137	15.62%		
>100	_	54	6.16%		
Median (IQR)	_	65.74 (55.8–76.95)	-		
Reported countries, n (%)	6692	_	100.00%		
US	_	5410	80.84%		
Non-US	-	1282	19.16%		
Indications, n (%)	3644	_	54.45%		
Breast cancer	_	1627	44.65%		
Breast cancer metastatic		939	25.77%		
Breast cancer female		405	11.11%		
Pik3ca related overgrowth spectrum	_	123	3.38%		
Pik3ca-activated mutation	_	100	2.74%		
Others	_	450	12.35%		
Combination drugs, n (%)	1931	_	28.86%		
Fulvestrant	_	619	32.06%		
Metformin	_	217	11.24%		
Faslodex	_	217	11.24%		
Letrozole	_	181	9.37%		
Kisqali	_	126	6.53%		
Outcomes, n (%)	6692	_	100.00%		
Non-serious Outcome	_	3172	47.40%		
Serious Outcome	_	3520	52.60%		
Death	_	945	26.85%		
Life-threatening	_	126	3.58%		
Hospitalization	-	1225	34.80%		
Disability	-	10	0.28%		
Other serious outcomes	-	1884	53.52%		
Time-to-onset (days)	631		9.43%		
Median (IQR)		20 (7–66)			
Reporters, n (%)	6334	_	94.65%		
Health professional	_	3178	50.17%		
Consumer	-	3156	49.83%		
Reporting year, n (%)	6692	_	100.00%		
2023Q1-Q2	-	899	13.43%		
2022	_	1752	26.18%		
2021	_	1686	25.19%		
2020	_	1653	24.70%		
2019Q2-Q4	_	702	10.49%		

and Empirical Bayes Geometric Mean (EBGM) methods. However, the SOC labeled as "General disorders and administration site conditions (SOC: 10018065, n = 2770)" demonstrated a positive signal using the ROR and IC methods, while this wasn't mirrored in the Proportional PRR and EBGM methods.

Additionally, we conducted disproportionality analysis at the PT, as presented in Supplementary Table S3. Not only that, based on the disproportionality analysis of PT, we further conducted analysis at gender, age, and whether concomitant drugs were used, as presented in Supplementary Table S4. And we had statistics on the Time-to-onset of AEs, which are presented in Supplementary Table S5.

In addition to the adverse drug reactions cataloged by the FDA, our study has unveiled a collection of unexpected AEs, including lip swelling, reflux gastritis, diverticulum intestinal, intra-abdominal fluid collection, tongue discomfort, bacteriuria, laryngitis viral, vulvovaginal candidiasis, blood chloride decreased, coma hepatic, feeding disorder, eating disorder, parosmia, cervix disorder, rectocele, allergic sinusitis, polyuria, pleural effusion, nail cuticle fissure, onychoclasis, and lymphoedema.

# 3.3. Characteristics of AE reports for different indications

Separate analyses for each indication were detailed in Table 3. Upon comparison of the overall clinical profiles between these two

# Table 2

Signal strength of reports of alpelisib at the System Organ Class (SOC) level in FAERS database.

SOC		Case number(n)	ROR (95%two-sided CI))	PRR (χ2)	IC (IC025)	EBGM (EBGM05)
General disorders and administration site conditions	2770	1.01	1.01 (0.34)	69.18 (66.40)	1.01	
		(0.97–1.05)			(0.97)	
Gastrointestinal disorders	2263	2.30	2.11 (1415.40)	0.93 (0.89)	2.11	
		(2.20–2.40)			(2.02)	
Metabolism and nutrition disorders	2053	6.49	5.78 (8247.25)	0.40 (0.38)	5.75	
Investigations	1711	(6.20-6.80)	1 08 (870 06)	1 01 (0.96)	(5.49)	
livestigations	1/11	(2.10)	1.90 (07 9.90)	1.01 (0.90)	(1.88)	
Skin and subcutaneous tissue disorders	1681	2.11	1.99 (871.50)	1.01 (0.96)	1.99	
		(2.00-2.22)		()	(1.89)	
Nervous system disorders	770	0.67	0.69 (119.93)	-1.83	0.69	
		(0.62–0.72)		(-1.97)	(0.64)	
Neoplasms benign, malignant and unspecified (incl	689	0.90	0.90 (7.99)	-6.61	0.90	
cysts and polyps)		(0.83–0.97)		(-7.13)	(0.83)	
Injury, poisoning and procedural complications	645	0.31	0.33 (975.83)	-0.63	0.33	
		(0.28–0.33)		(-0.68)	(0.31)	
Infections and infestations	495	0.54	0.55 (190.64)	-1.17	0.55	
Descinctory description days direction lateration	160	(0.49–0.59)	0 (0 ((5 05)	(-1.28)	(0.51)	
Respiratory, thoracic and mediastinal disorders	460	0.68	0.69 (65.25)	-1.89	0.69	
Musculoskeletal and connective tissue disorders	300	(0.02-0.73)	0.58 (127.70)	(-2.06)	0.58	
Musculoskeietai and connective ussue disorders	377	(0.51_0.63)	0.30 (127.70)	(-1.40)	(0.52)	
Psychiatric disorders	311	0.41	0.42 (260.68)	-0.80	0.42	
i sy chiadre disordero	011	(0.37–0.46)	0112 (200100)	(-0.90)	(0.38)	
Renal and urinary disorders	246	0.75	0.75 (20.59)	-2.43	0.75	
		(0.66-0.85)		(-2.76)	(0.66)	
Immune system disorders	188	0.75	0.75 (15.23)	-2.46	0.75	
		(0.65–0.87)		(-2.85)	(0.65)	
Eye disorders	185	0.65	0.65 (34.50)	-1.63	0.65	
		(0.56–0.75)		(-1.89)	(0.57)	
Vascular disorders	183	0.48	0.49 (100.92)	-0.97	0.49	
Discission discussions	150	(0.42-0.56)	0.51 (70.00)	(-1.12)	(0.42)	
Blood and lymphatic system disorders	153	0.51	0.51 (72.96)	-1.03	0.51	
Surgical and medical procedures	146	0.51	0 52 (66 46)	(-1.21) -1.06	0.52	
Surgical and metical procedures	140	(0.44 - 0.60)	0.32 (00.40)	(-1.24)	(0.44)	
Hepatobiliary disorders	132	0.88	0.88 (2.04)	-5.61	0.88	
· · · · · · · · · · · · · · · · · · ·		(0.74-1.05)		(-6.65)	(0.74)	
Product issues	78	0.23	0.23 (203.21)	-0.47	0.23	
		(0.18-0.28)		(-0.59)	(0.19)	
Cardiac disorders	75	0.21	0.22 (218.34)	-0.45	0.22	
		(0.17–0.27)		(-0.57)	(0.17)	
Reproductive system and breast disorders	59	0.51	0.51 (28.04)	-1.03	0.51	
		(0.39–0.66)		(-1.33)	(0.39)	
Congenital, familial and genetic disorders	40	0.92	0.92 (0.31)	-7.92	0.92	
For and laborate disorders	24	(0.67–1.25)	0 40 (07 60)	(-10.81)	(0.67)	
Ear and labyrinth disorders	34	0.42	0.42 (27.62)	-0.80	0.42	
Endocrine disorders	11	0.21	0.21 (31.91)	-0.45	0.21	
Lastane aborders	**	(0.12 - 0.39)	01.71)	(-0.81)	(0.12)	
Social circumstances	11	0.11	0.11 (75.72)	-0.32	0.11	
		(0.06-0.21)	. ,	(-0.58)	(0.06)	

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio;  $\chi^2$ , chi-information component; IC, information component; IC025, the lower limit of 95% CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

groups, significant disparities emerged in terms of gender distribution, age distribution, weight, and the incidence of severe outcomes. In both groups, the number of female patients far exceeded that of males. However, when it came to age, the median value for the PROS group (14 years) was markedly lower than that for the PIK3CA-mutated breast cancer group (63 years). We further examined outcome indicators for all patients. The death toll was more for the PIK3CA-mutated breast cancer group (n = 390) compared to the PROS group (n = 0). The population of life-threatening was more for the PROS group (n = 75) than for the PIK3CA-mutated breast cancer group (n = 4).

#### Y. Lin et al.

Clinical information associated with specific indications.

	PIK3CA-mutated breast cancer	PIK3CA-related overgrowth spectrum
Total	3138	123
Gender, n (%)	_	_
Female	2938 (98.76%)	66 (61.68%)
Male	37 (1.24%)	41 (38.32%)
Age (years), n (%)	_	_
<18	1 (0.07%)	49 (58.33%)
$18 \le and \le 65$	797 (53.71%)	34 (40.48%)
>65	686 (46.23%)	1 (1.19%)
Median (IQR)	63(55–71)	14(7-28)
Weight (Kg), n (%)	_	_
<80	487 (78.17%)	29 (74.36%)
80 < and <100	92 (14.77%)	7 (17.95%)
>100	44 (7.06%)	3 (7.69%)
Median (IQR)	66.68 (56.1–76.72)	56.4 (40-80)
Reported countries, n (%)	_	_
US	2009 (64.02%)	94 (76.42%)
Other country	1129 (35.98%)	29 (23.58%)
Outcomes, n (%)	_	_
Non-serious Outcome	1191 (37.95%)	70 (56.91%)
Serious Outcome	1947 (62.05%)	53 (43.09%)
Death	390 (20.03%)	0 (0.00%)
Life-threatening	75 (3.85%)	4 (7.55%)
Hospitalization	780 (40.06%)	24 (45.28%)
Disability	26 (1.34%)	1 (1.89%)
Other serious outcomes	1128 (57.94%)	38 (71.70%)
Time-to-onset (days)	415 (13.22%)	37 (30.08%)
Median (IQR)	21 (9–68)	5 (0–75)
Reporters, n (%)	-	-
Health professional	1813 (60.21%)	68 (55.28%)
Consumer	1198 (39.79%)	55 (44.72%)
Reporting year, n (%)	-	-
2023Q1-Q2	432 (13.77%)	66 (53.66%)
2022	888 (28.30%)	40 (32.52%)
2021	914 (29.13%)	14 (11.38%)
2020	587 (18.71%)	3 (2.44%)
2019Q2-Q4	317 (10.10%)	0 (0.00%)

# 3.4. Adverse reaction frequency analysis

PTs related to different indications of alpelisib were excluded from the analysis and then ranked in descending order based on their frequency and ROR. Table 4 presents the top significant safety signals individually. We then conducted a comparison with the adverse reactions specified in the drug instructions, using an asterisk (\*) to denote those not mentioned in the instructions.

# 4. Discussion

Drawing upon the extensive dataset within the FAERS database, our study offers a comprehensive analysis of the real-world safety profile of alpelisib. According to the characteristics of AE reports, an upward trajectory emerges in the number of reported AEs in FAERS as the years progress, which may be related to the increase in the number of patients treated by alpelisib. Given alpelisib's primary application in the treatment of advanced breast cancer, it follows that a greater number of AE reports in FAERS pertains to adult females. However, due to the absence of accurate patient numbers using alpelisib, it remain further study that which groups of patients are more likely to have AEs.

The findings of our study underscore a clustering of common SOCs around gastrointestinal disorders, metabolism and nutrition disorders, investigations, as well as skin and subcutaneous tissue disorders. Additionally, frequently reported PTs associated with alpelisib include hyperglycemia, rash, nausea, fatigue, decreased appetite, weight loss, stomatitis, and dehydration. Notably, these AEs are in accordance with information provided in the FDA's drug label and previous research on alpelisib.

For instance, a randomized phase III clinical study combining PI3K inhibitor alpelisib with fulvestrant identified hyperglycemia, rash, and diarrhea as the most common grade 3/4 AEs [9]. Similarly, a post-marketing study based on the World Health Organization pharmacovigilance database highlighted hyperglycemia, rash, diarrhea, increased blood glucose, and nausea as the most frequently reported AEs [16]. Moreover, an analysis of alpelisib's safety profile in breast cancer patients identified rash as a predominant AE, primarily affecting the trunk (78%) and extremities (70%), typically emerging within two weeks of treatment initiation [17]. This alignment of our study and previous research reinforces the significance of these findings and their applicability in real-world clinical scenarios.

In addition to known AEs, our study unearthed unexpected AEs that were not provided in FDA label. These include lip swelling,

# Table 4

Top significant signals on the PT level (\*: The instruction does not mention).

$\begin{array}{ c c c c c c c c c c c c c c c c c c c$	SOC	РТ	Case	ROR (95% two-sided	PRR ( $\chi^2$ )	IC	EBGM
PHESCA investigations inves			number(n)	CI)		(IC025)	(EBGM05)
Investigations and inferations	PIK3CA-mutated breast cancer						
$ \begin{array}{ c c c c c c c c c c c c c c c c c c c$	Investigations	Tumour marker decreased	16	295.66	295.29	0.13	248.20
Intension and infestations in first and in the state in t	T	Contratoria anti- and 15.0	2	(173.17–504.79)	(3941.86)	(0.07)	(145.38)
Intervals     Larngetix viral*     5     21.6.40     21.5.31     0.13     0.019       Skin and subctaneous itsue     Nail cuile fissure*     1     160.41     160.37     0.14     15.35       disorders     (48.86-23.66)     (43.05.99)     0.14     14.12.2       disorders     (47.32-20.81.16)     (17.33)     0.14     14.12.2       disorders     (47.32-20.81.16)     (17.33)     0.14     14.12.2       disorders     (47.32-20.81.16)     0.14     11.4.22     (17.30)     0.15     11.1.74       disorders     Proprintive system and     Proprintive system and nutrition	Investigations	Carbohydrate antigen 15-3	3	232.59	232.54	0.13	202.34
bit and subcuraneous tissue disorders     Bail cuicie fisuers*     P     (94.37–948.99)     (99.5.23)     (0.04)     (14.37)       disorders     Bail cuicie fisuers*     P     (16.37)     (14.43)     (14.43)       disorders     Calification metastric     P     (15.03)     (14.43)     (14.42)       disorders     P     (14.37)     (14.43)     (14.43)     (14.43)     (14.43)       disorders     P     (14.33)     (14.44)     (14.42)     (14.43)     (14.42)       disorders     P     (14.53)     (14.53)     (14.53)     (14.53)     (14.53)     (14.53)       disorders     P     (14.53) <td>infections and infestations</td> <td>Larvagitic viral*</td> <td>5</td> <td>(09.11-782.85) 215.40</td> <td>(001.42)</td> <td>(0.04)</td> <td>(00.12)</td>	infections and infestations	Larvagitic viral*	5	(09.11-782.85) 215.40	(001.42)	(0.04)	(00.12)
Skin and subcutaneous itsue disorders     Nail cuicle fissure*     3     100.41     100.37     0.14     105.37       Matabolism and nutrition disorders     Calefication metastatic     3     155.06     155.03     0.04     11.01.21       Matabolism and nutrition disorders     Ryperglyseemia     789     143.31     134.40     0.44     123.76       Generation for the statution disorders     PRECA-sclwated mutation     17     120.50     120.34     0.15     11.14       generic disorders     Retoecle*     5     81.62     81.87     0.16     77.56       Prest disorders     Hyperglyseemia hopersonolar     20     68.86     0.875     0.17     65.87       Invest guitors     Tumour mayber abnormal     8     65.027.00     0.527.01     0.18     50.63       Nervous system disorders     Canbolyntar atingta 15.3     0.00     (21.91-32.13)     0.00     (23.91     0.18     50.63       Nervous system disorders     Cambolyntar atingta 15.3     0.10     (27.91-131.12)     0.00     (0.30,00     (23.92,00)     (23.92,00)     (23.92,00)		Laryingitis virai	5	(84.51-548.99)	(936.52)	(0.05)	(74.22)
isorders Galdingtion metatatic (48.8-526.66) (60.25) (0.40) (41.02)   isorders Congenital, familial and sprote system Pyperglycaemia 72 (12.9-514.40) (41.7.36) (0.40) (13.40)   isorders Pyperglycaemia Pyperglycaemia (12.9-514.40) (13.40) (13.40) (13.40) (13.40)   isorders Pyperglycaemic system Pyperglycaemic system (13.24) (13.40) (13	Skin and subcutaneous tissue	Nail cuticle fissure*	3	160.41	160.37	0.14	145.43
Ideabalism and nutrin Calibration extention 3 15.06 15.06 15.06 141.02   disorders 15.06 (417.35) (0.04) 12.376   disorders 12.320-515.4197.41 (96182.32) (0.16) (1.5)   genetic disorders 17 (12.50-197.44) (1867.02) (0.05) (1.5)   Reproductive system and matrin Hypersystemic hyperomalic 20 68.30 (0.77) (0.06) (1.5)   Investigations Hypersystemic hyperomalic 20 68.30 (0.37) (1.0) (0.6)   Investigations Tumour marker abnormal 20 68.30 (0.37) (0.00) (0.38)   Investigations Carbelydres antigon 15.3 (1.4) (1.5) (0.6) (0.6) (0.6)   Investigations Carbelydres antigon 15.3 (1.4) (1.5) (0.6) (0.6) (0.6)   Investigations Carbelydres antigon 15.3 (1.6) (0.6) (0.6) (0.6) (0.6)   Investigations Carbelydres antigon 15.3 (1.6) (1.6) (1.6) (1.6) (0.6) (1.7)   Idisorders Carbelydres antigon 15.3 (1.6) (0.6) (1.7) (1.6) (1.6) (1.6) (1.6) </td <td>disorders</td> <td></td> <td></td> <td>(48.86-526.66)</td> <td>(430.59)</td> <td>(0.04)</td> <td>(44.30)</td>	disorders			(48.86-526.66)	(430.59)	(0.04)	(44.30)
instruction Mictability and mutrition instructions instructions instructions instructions instructions instructions instructions instructions instructions(47.33-14.33.1) (132.96-15.44.66)(43.33) (132.96-15.44.66)(43.33) (132.96-15.44.66)(43.33) (132.96-15.44.66)(43.33) (132.96-15.46)(43.33) (132.96-15.46)(43.33) (132.96-15.46)(43.33) (132.96-15.46)(43.33) (132.96-15.46)(43.33) (132.96-15.46)(43.33) (132.96-15.46)(43.33) 	Metabolism and nutrition	Calcification metastatic	3	155.06	155.03	0.14	141.02
Metabolism and nutrition     Hyperglycaemia     789     143.31     134.40     0.14     123.76       disorders     PR3CA-activated mutation     17     120.50     120.34     0.15     11.174       genetic disorders     Reproductive system and     Rectocele*     5     81.62     81.50     0.16     77.56       Metabolism and nutrition     Hyperglycaemic hypersonolar     20     68.86     68.75     0.17     65.87       Investigations     Tumour marker abnormal     8     65.32     0.127.58     0.010     62.68       Metabolism and nutrition     Investigations     Tumour marker abnormal     8     65.32     0.17     62.68     0.000     10.00     0.003 <t< td=""><td>disorders</td><td></td><td></td><td>(47.32–508.16)</td><td>(417.36)</td><td>(0.04)</td><td>(43.03)</td></t<>	disorders			(47.32–508.16)	(417.36)	(0.04)	(43.03)
disorders     (13296-134.46)     (981822)     (0.13)     (114.82)       Congenital, familial and genetic disorders     PR3CA-activated mutation     (72.34-197.4)     (186.20)     (0.00)     (68.20)       Reproductive system and matrixito     Retrocele*     5     81.62     81.59     0.16     (77.56)       breast disorders     Herabolian duritrition     Hyperomatic hyperomanic     (63.20)     (62.7)     0.010     (63.76)       investigations     Tumour marker abnormal     8     (63.20)     (63.76)     0.010     (62.76)       investigations     Cambolydrate antigen 15-3     11     52.35 (28.70-95.50)     52.31     0.18     50.63       Skin and shortrition     increased     Combolydrate antigen 15-3     11     43.46     0.18     47.01       disorders     Increased     Combolydrate antigen 15-3     14     43.46     0.48     0.18     43.00       disorders     Increased     Indras 14.57     10.00     (63.72)     0.01     10.74       disorders     Increased     Indras 14.51     10.18     34.90     11.92 </td <td>Metabolism and nutrition</td> <td>Hyperglycaemia</td> <td>789</td> <td>143.31</td> <td>134.40</td> <td>0.14</td> <td>123.76</td>	Metabolism and nutrition	Hyperglycaemia	789	143.31	134.40	0.14	123.76
Congenital familiant of particulation function     17     120.50     120.43     0.13     111.74       Reproductive system and productive system and function     Fectoccle*     5     81.62     81.52     81.59     0.16     77.56       Metabolisn and nutrition     Hyperglycaemic hyperosmolar and text system function     8     65.32     0.05     0.17     65.87       Metabolisn and nutrition     Hyperglycaemic hyperosmolar and text system function     8     65.32     0.13     65.87     0.17     65.87       Nervous system disorders     Tumour marker absormal     8     62.32     0.23     0.03     0	disorders		17	(132.96–154.46)	(96182.52)	(0.13)	(114.82)
agenus based and particle system and partic	Congenital, familial and	PIK3CA-activated mutation	17	120.50	120.34	0.15	(68.20)
besart disorderincreased $(33,20-200,66)$ $(37,3)$ $(00,6)$ $(31,35)$ Metabolism and nutritionindexotic syndrome20 $(63,86-107,80)$ $(22,53)$ $(0,11)$ $(42,06)$ InvestigationsTumour marker abnormal8 $(53,27-05,50)$ $(53,23)$ $(0,11)$ $(42,06)$ Nervous syndromic disordersCarbolydrate antigen 15.31 $22,35(28,70-55,50)$ $(53,55)$ $(0,10)$ $(27,77)$ Sin and subcitaneous tissueCarbolydrate antigen 15.31 $22,35(28,70-55,50)$ $(53,55)$ $(0,10)$ $(7,77)$ disordersDermal absorption impaired3 $43,16$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,64$ $48,56$ $(13,37)$ $(1$	Reproductive system and	Bectocele*	5	(73.34-197.44)	(1007.02) 81.59	0.16	77 56
Introbaliss and nutrition     Hyperglycaemic hypersonalar     63.86     63.87     0.17     65.87       disorders     nonkertic syndrome     63.38-07.80     62.37     0.110     (42.08)       Investigations     Tumour marker abnormal     8     63.32     65.37     0.110     (42.08)       Investigations     Carbohydrate antigen 15-3     11     52.35 (28.70-95.05)     52.31     0.18     50.63       Skin and abutchancous tisse     increased     10.00     (17.91-131.12)     (180.23)     0.100     (27.95)       disorders     menal absorption impaired     4     48.46     48.45     0.18     43.90       disorders     paral absorption impaired     24     40.00 (26.66-60.00)     90.20     0.130     (25.96)       mediastinal disorders     Nata Increased     31.22 (9.95-97.92)     1.21 (86.01)     0.00     0.01 (27.90)       disorders     Arophic vulvoraginitis     3     32.29 (9.57-94.09)     0.010 (25.20)     0.00     0.027       disorders     Arophic vulvoraginitis     3     22.99 (9.50-97.20)     1.21 (86.00)     0.01 <td>breast disorders</td> <td>heerotele</td> <td>5</td> <td>(33.20-200.66)</td> <td>(378.13)</td> <td>(0.06)</td> <td>(31.55)</td>	breast disorders	heerotele	5	(33.20-200.66)	(378.13)	(0.06)	(31.55)
Investigations number of participants (3.98-107.80) (1.278.58) (0.11) (4.208.10)   Investigations Tumour marker abnormal 8.0 (5.23 (6.278.0) (8.488.68) (0.10) (2.78.11)   Nervous system disorders Carbohydrate antigen IS-3 1.1 (2.38.12.12) (8.48.68) (8.18) (8.18)	Metabolism and nutrition	Hyperglycaemic hyperosmolar	20	68.86	68.75	0.17	65.87
InvestigationsTunour marker abnormal86.5.26.5.20.1062.28Investigations(221-91-232)(485.86)(0.0800.89Nervous system disorders(archolydrate antigen 15-3)1.15.25.28.70-95.09(2.31)0.185.03Skin and subtraincour tissue(archolydrate antigen 15-3)1.15.25.28.70-95.09(0.18)(1.7)(1.7)disorders(archolydrate antigen 15-3)(1.7)(1.8)4.84.500.18(1.7)(1.7)disordersPolydipsia(1.7)(1.4)(1.8)(1.6)(1.3) <t< td=""><td>disorders</td><td>nonketotic syndrome</td><td></td><td>(43.98–107.80)</td><td>(1278.58)</td><td>(0.11)</td><td>(42.08)</td></t<>	disorders	nonketotic syndrome		(43.98–107.80)	(1278.58)	(0.11)	(42.08)
Invertigations(Carbolydrate antigen 15.3)(Carbolydrate antigen 15.3)	Investigations	Tumour marker abnormal	8	65.32	65.27	0.17	62.68
Nervous system disorders     Gardohydrate antigen 15-3     11     52.35 (28.70-95.50)     52.31     0.18     50.63       Skin and subturaneous tissue     Gardohydrate antigen 15-3     4     48.46     48.45     0.18     47.01       Metabolism and nutrition     (T7.91-131.2)     (18.03.0)     (0.77)     (17.37)       disorders     Dermal absorption impaired     3     45.16     45.15     0.18     43.90       Respiratory, thoracic and     Phydipsia     24     40.00 (26.66-60.00)     99.92     0.19     38.94       Reproductive system and     Nasal mecoal disorder     3     31.22 (9.95-97.92)     31.21 (86.01)     0.20     20.56 (87.60)       Investigations     Tumour marker increased     3     30.01 (9.57-94.09)     9.0.01 (82.52)     0.20     29.45 (8.40)       Investigations     Tumour marker increased     3     25.96 (8.30-81.33)     25.96 (70.78)     2.12 (5.70.80)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.12 (5.70.8)     2.10.21 (5.70.8)	Investigations			(32.19–132.53)	(485.86)	(0.08)	(30.89)
Skin and subcutaneous tissue     increased     Coma hepati*     4     8.46     (335.35)     (0.10)     (27.76)       Misebablism and nutrition	Nervous system disorders	Carbohydrate antigen 15-3	11	52.35 (28.70–95.50)	52.31	0.18	50.63
mode of the system and nutrition     Control and particle     4     48-85     48-85     0.18     41/01       Metabolism and nutrition     (17.91-131.12)     (18.02.3)     (0.17)     (17.37)       disorders     Dermal absorption impaired     3     45.16     45.15     (0.01)     (13.33)       Respiratory, thoracic and     Particle absorption impaired     3     45.16     (13.33)     (25.96)       Reproductive system and infectations     Nasal mucosal disorder     3     34.46     34.45 (95.32)     0.20     30.52 (97.6)       Investigations     Arrophic vulvovaginitis     3     31.22 (9.95-97.92)     31.21 (86.01)     0.20     20.42 (97.6)       Investigations     Tumour marker increased     3     30.01 (9.57-94.09)     30.01 (82.52)     0.20     20.43 (9.40)       Infections and infestations     Tumour marker increased     3     25.59 (8.30-81.35)     25.58 (7.07)     0.11     25.57 (8.17)       Infections and infestations     Tumour marker increased     3     2.52 (8.08-97.12)     2.52 (8.08,3)     0.22     2.48 (7.95)       Infections and infestations     Gastrin	Skin and subcutaneous tissue	increased		10.16	(535.55)	(0.10)	(27.76)
metabolism and muturing     permal absorption impaired $1000000000000000000000000000000000000$	disorders Matcheliem and putrition	Coma hepatic*	4	48.46	48.45	0.18	47.01
label and body in the bod	disorders	Dermal absorption impaired	3	(17.91–131.12) 45.16	(180.23) 45.15	(0.07)	(17.37)
mediastinal disorders     Polydipsia     24     40.00 (26.66-60.00)     39.92     0.19     38.94       Reproductive system and     Nasal mucosal disorders     Nasal mucosal disorders     (10.797-108.20)     (0.06)     (10.74)       Metabolism and nutrition     Atrophic vulvovaginitis     3     31.22 (0.95-779.400)     0.01 (82.52)     0.02     29.45 (9.40)       Investigations     Tumour marker increased     35     27.56 (19.72-38.52)     27.49     0.21     27.03       Gastrointestinal disorders     Tumour marker increased     35     25.99 (8.30-81.35)     25.98 (70.87)     0.21     25.70 (0.77)       Investigations     Bacteriuria*     3     25.28 (8.08-79.12)     25.28 (6.8.33)     0.22     24.89 (7.95)       Investigations     Bacteriuria*     3     23.98 (7.67-75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Investigations     Bone lesion*     15     23.03 (13.83-38.35)     23.00     0.22     22.68       Kis and subcutaneous tissue     disorders     Nutritional condition abnormal     3     22.15 (7.09-69.25)     22.15 (5.07.2)     22.18 (5.6.91)     0.0	Respiratory, thoracic and	Dermai absorption impaired	5	(14.33–142.37)	(125.86)	(0.06)	(13.93)
Reproductive system and breast disorders     Nasal mucosal disorder     3     34.46     (887.88)     (0.13)     (25.96)       Metabolism and nutrition disorders     Atrophic vulvovaginitis     3     31.22 (9.95-97.92)     31.21 (86.01)     0.20     30.62 (9.76)       Investigations     Reproductive system and breast disorders     Hypermetabolism <sup>4</sup> 3     30.01 (9.57-94.09)     30.01 (82.52)     0.20     29.45 (9.40)       Investigations     Tumour marker increased     35     27.56 (19.72-38.52)     27.49     0.21     27.03       Gastrointestinal disorders     Tumour marker increased     35     25.98 (80.8-13.5)     25.98 (70.87)     0.21     25.57 (8.17)       Investigations     Bacteriuria*     3     25.99 (8.30-81.35)     25.98 (70.87)     0.21     25.57 (8.17)       Investigations     Bacteriuria*     3     25.28 (80.8-79.12)     25.28 (80.83)     0.22     26.62 (7.55)       Nervous system disorders     Gingival erythema     3     23.09 (13.83-38.35)     23.00     0.22     22.68       Nervous system disorders     Nutritional condition abnormal     3     21.57 (7.9-69.25)	mediastinal disorders	Polydipsia	24	40.00 (26.66–60.00)	39.92	0.19	38.94
Impact disorders     Nasal mucosal disorder     3     34.46     34.45 (95.32)     0.03     33.72       Merabolism and nutrition     Arrophic vulvovaginitis     3     31.22 (9.95-97.22)     31.21 (86.01)     0.02     30.62 (9.7.6)       Reproductive system and     Hypernetabolism*     3     31.22 (9.95-97.22)     31.21 (86.01)     0.20     2.45 (9.4.0)       Reproductive system and     Hypernetabolism*     3     7.55 (19.72-38.52)     2.749     0.210     7.03       Reproductive system and infestatons     Tumour marker increased     3     2.59 (8.0-8.7.8)     2.749     0.210     2.507 (8.7.7)       Musculoskeletal and     Cervix disorder*     3     2.528 (8.08-7.9.12)     2.528 (8.6.8.3)     2.007     0.070     0.307     0.210     2.507 (8.7.7)       Investigations     Bacteriuria*     -     2.258 (8.0.8-7.9.12)     2.508 (8.5.9)     0.070     0.230     2.480     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.707     0.7	Reproductive system and	5 I			(887.88)	(0.13)	(25.96)
Metabolism and nutrition     (10.97-108.20)     (0.06)     (0.074)       disorders     Atrophic vulvovaginitis     3     31.22 (9.95-97.92)     31.21 (86.01)     0.20     20.26 (9.76)       Reproductive system and     Hypermetabolism*     3     0.01 (9.57-94.09)     30.01 (8.25.20)     0.20     29.45 (9.40)       Infections and infestations     Tumour marker increased     3     27.56 (19.72-38.52)     27.49     0.15 (19.74)     (0.15)     (0.37)       Gastrointestinal disorders     Immour marker increased     3     25.98 (8.08-912)     25.98 (70.87)     0.21     25.57 (8.17)       Connective tissue disorders     Enteritria*     3     25.28 (8.08-912)     25.28 (6.81)     0.22     24.89 (7.95)       Investigations     Gigival crythema     3     23.03 (13.83-83.53)     23.00     0.22     26.82 (5.55)       Blood and hymphatic system     Gigival condition abnormal     3     21.15 (7.09-69.25)     21.15 (7.91)     21.48 (7.97)       Investigations and infestations     Diabetic coma     3     21.15 (7.09-69.25)     21.55 (9.18.31)     22.30 (18.83 - 49)       Gisorders     Intre	breast disorders	Nasal mucosal disorder	3	34.46	34.45 (95.32)	0.20	33.72
Idisorders     Arrophic vulvovaginitis     3     31.22 (9.59-57.92)     31.21 (86.01)     0.20     30.26 (9.76)       Investigations	Metabolism and nutrition			(10.97–108.20)		(0.06)	(10.74)
Investigations	disorders	Atrophic vulvovaginitis	3	31.22 (9.95–97.92)	31.21 (86.01)	0.20	30.62 (9.76)
here at the productive system and infestations     rypermetabolism     3     3001 $(9,3,-94,09)$ 0.00 $(8,2,3)$ 0.20     29.48 $(9,40)$ Infections and infestations     Tumour marker increased     35     27.56 $(19,72-38.52)$ 27.49     0.21     25.76 $(19,72-38.52)$ Musculoskeletal and connective tissue disorders     Cervix disorders*     3     25.99 $(8.30-81.35)$ 25.98 $(70,70,87)$ 0.21     25.76 $(19,72-38.52)$ Investigations     Bacteriuria*     3     25.28 $(80,8-79.12)$ 25.28 $(68.33)$ 0.22     24.89 $(7.57)$ Investigations     Bacteriuria*     3     23.98 $(7.67-75.01)$ 23.97 $(65.04)$ 0.22     21.82 $(7.55)$ Investigations     Bone lesion*     15     23.03 $(13.83-38.35)$ 23.00     0.22     21.85 $(6.99)$ Investigations     Nutritional condition abnormal     3     22.15 $(7.09-69.25)$ 22.15 $(57.72)$ 0.22     21.85 $(6.99)$ Hepatobiliary disorders     Nutritional condition abnormal     3     22.15 $(7.09-69.25)$ 21.15 $(57.72)$ 0.22     21.85 $(6.90)$ Hepatobiliary disorders     Nutritional conditions	Investigations	TT	2	00.01 (0.57.04.00)	00.01 (00.50)	(0.06)	00.45 (0.40)
Infections and infestations     Tumour marker increased     35     27.56 (19.72-38.52)     27.49     0.21     27.03       Gastrointestinal disorders     Gastrointestinal disorders     (0.15)     (19.34)       Musculoskeletal and     Cervix disorder*     3     25.99 (8.08-81.35)     25.98 (70.87)     0.21     25.57 (8.17)       Investigations     Bacteriuria*     3     25.28 (8.08-7.91.2)     25.28 (68.88)     0.22     23.62 (7.55)       Nervous system disorders     Gingival erythema     3     23.98 (7.67-75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Blood and lymphatic system     Gingival erythema     3     23.03 (13.83-38.35)     23.00     0.22     22.68       Skin and subcutaneous tissue     15     23.03 (13.83-38.35)     23.00     0.22     23.68 (7.57)       Hepatobiliary disorders     Nutritional condition abnormal     3     22.15 (7.09-69.25)     22.15 (59.72)     0.21 (9.7)     20.30 (8.40)       Hepatobiliary disorders     Nutritional condition abnormal     3     12.17 (58.2-56.72)     18.17 (8.10)     0.24     17.97 (8.7)       Respiratory, thoracic and mifestations </td <td>Reproductive system and</td> <td>Hypermetabolism*</td> <td>3</td> <td>30.01 (9.57–94.09)</td> <td>30.01 (82.52)</td> <td>0.20</td> <td>29.45 (9.40)</td>	Reproductive system and	Hypermetabolism*	3	30.01 (9.57–94.09)	30.01 (82.52)	0.20	29.45 (9.40)
Intercent interaction     Function interaction     For (FAP 2 000)     For (FAP 2 000)     (B77, 84)     (D15)     (19.34)       Musculoskeletal and connective tissue disorders     Cervix disorder*     3     25.98 (8.08–79.12)     25.98 (6.8.33)     0.21     25.57 (8.17)       Investigations     Bacteriuria*     3     25.28 (6.8.79.12)     25.28 (6.8.83)     0.22     24.89 (7.95)       Nervous system disorders     Gingival erythema     3     23.98 (7.67–75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Blood and lymphatic system     Gingival erythema     3     23.03 (13.83–38.35)     23.00     0.22     21.85 (6.99)       Investigations     Bone lesion*     15     20.307 (8.51–49.71)     20.56 (91.83)     0.23     20.30 (8.40)       disorders     Nutritional condition abnormal     3     21.57 (7.9–69.25)     22.15 (59.72)     0.22     21.85 (6.99)       Hepatobiliary disorders     Diabetic coma     5     20.57 (8.51–49.71)     20.56 (91.83)     0.23     20.30 (8.40)       administration site conditions     Increased     10.10     7     17.91     0.24     17.7	Infections and infestations	Tumour marker increased	35	27 56 (19 72-38 52)	27 49	0.21	27.03
Musculoskeletal and constructive disorders     Cervix disorders*     3     25.99 (8.30–81.35)     25.98 (70.87)     0.21     25.57 (8.7)       Investigations     Bacteriuria*     3     25.28 (8.08–79.12)     25.28 (68.83)     0.22     24.89 (7.95)       Blood and lymphatic system     Gingival erythema     3     23.98 (7.67–75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Blood and lymphatic system     Gingival erythema     3     23.03 (13.83–38.35)     23.00     0.22     22.68 (6.99)       Investigations     Bone lesion*     15     23.03 (13.83–38.35)     23.00     0.22     21.85 (6.99)       Hepatobiliary disorders     Nutritional condition abnormal     3     22.15 (7.09–69.25)     22.15 (59.72)     0.22     21.85 (6.99)       General disorders     Nutritional condition abnormal     3     18.17 (5.82–56.72)     18.17 (48.10)     0.24     17.97 (5.76)       Infections and infestations     Garcinoembryonic antigen     7     17.92 (8.50–37.75)     17.91     0.24     17.97 (5.76)       Infections and infestations     Carcinoembryonic antigen     7     16.30 (7.74–34.34)     16.29 (99.4	Gastrointestinal disorders	runour marker mercasea	00	27.00 (19.72 00.02)	(877.84)	(0.15)	(19.34)
connective tissue disorders     0.07     (0.07)       Investigations     Bacteriuria*     3     25.28 (8.08-79.12)     25.28 (8.68.3)     0.22     24.89 (7.95)       Nervous system disorders     Gingival erythema     3     23.98 (7.67-75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Blood and lymphatic system     Gone lesion*     15     23.03 (13.83-38.35)     23.00     0.22     21.85 (6.99)       Investigations     Bone lesion*     15     23.03 (13.83-38.35)     23.00     0.22     21.85 (6.99)       Skin and subcutaneous tissue     Nutritional condition abnormal     3     20.57 (8.51-49.71)     20.56 (91.83)     0.22     21.85 (6.99)       Hepatobiliary disorders     General disorders and     Diabetic coma     5     20.57 (8.51-49.71)     20.56 (91.83)     0.23     20.30 (8.40)       administration site condition     Garcinoembryonic antigen     7     18.17 (5.82-56.72)     18.17 (48.10)     0.24     17.97 (5.76)       Infections and infestations     Garcinoembryonic antigen     7     16.81 (10.69-26.42)     16.78     0.25     16.61 (0.57)       Infections and infe	Musculoskeletal and	Cervix disorder*	3	25.99 (8.30-81.35)	25.98 (70.87)	0.21	25.57 (8.17)
Investigations     Bacteriuria*     3     25.28 (8.08–79.12)     25.28 (6.8.3)     0.22     24.89 (7.95)       Nervous system disorders     Gingival erythema     3     23.98 (7.67–75.01)     23.07 (65.04)     0.22     23.62 (7.55)       Blood and lymphatic system disorders     Bone lesion*     15     23.03 (13.83–83.35)     23.00     0.22     22.68       Skin and subcutaneous tisue     Nutritional condition abnormal     3     22.15 (7.09–69.25)     22.15 (59.72)     0.22     21.85 (6.99)       Hepatobiliary disorders     Nutritional condition abnormal     3     22.15 (7.09–69.25)     22.15 (9.72)     0.22     21.85 (6.99)       General disorders and administration site conditions     Diabetic coma     5     20.57 (8.51-49.71)     20.56 (91.83)     0.22     20.30 (8.40)       Respiratory, thoracic and mediastinal disorders     Iabetic coma     7     18.17 (5.82–56.72)     18.17 (48.10)     0.24     17.71 (8.41)       Infections and infestations     Carcinembryonic antigen increased     16.81 (10.69–26.42)     16.92     0.25     16.13 (7.69)       Infections and infestations     Carcinemenery     16.31 (7.43–34.34) <t< td=""><td>connective tissue disorders</td><td></td><td></td><td></td><td></td><td>(0.07)</td><td></td></t<>	connective tissue disorders					(0.07)	
Nervous system disorders     (0.07)       Blood and lymphatic system disorders     Gingival erythema     3     23.98 (7.67–75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Investigations     Bone lesion*     15     23.03 (13.83–38.35)     23.00     0.22     22.68       Skin and subcutaneous tissur     15     23.03 (13.83–38.35)     23.00     0.22     21.65 (0.91)       Hepatobiliary disorders     Nutritional condition abnormal     3     22.15 (7.09–69.25)     22.15 (59.72)     0.20     21.85 (0.99)       General disorders and     Diabetic coma     5     20.57 (8.51–49.71)     20.56 (91.83)     0.23     20.30 (8.40)       administration site condition     Furphadenopathy     3     18.17 (5.82–56.72)     18.17 (48.10)     0.24     17.97 (57.6)       mediastinal disorders     Infections and infestations     Carcinoembryonic antigen     7     17.92 (8.50–37.75)     17.91     0.24     17.97 (58.76)       Infections and infestations     Carcinoembryonic antigen     7     16.30 (7.74–34.34)     16.29 (9.45)     0.25     16.61       Inferetions and infestations     Mucosal dryness	Investigations	Bacteriuria*	3	25.28 (8.08–79.12)	25.28 (68.83)	0.22	24.89 (7.95)
Blood and lymphatic system disorders     Gingival erythema     3     23.98 (7.67–75.01)     23.97 (65.04)     0.22     23.62 (7.55)       Investigations     Bone lesion*     15     23.03 (13.83–38.35)     23.00     0.22     22.68       Skin and subcutaneous tissue     Investigations     Nutritional condition abnormal     3     22.15 (7.09–69.25)     22.15 (5.99.10)     0.20     22.68       Hepatobiliary disorders     Introduction abnormal     3     22.57 (8.51–49.71)     20.56 (91.83)     0.23     20.30 (8.40)       administration site conditions     Diabetic coma     5     20.57 (8.51–49.71)     20.56 (91.83)     0.24     17.97 (5.76)       mediastinal disorders     Hilar lymphadenopathy     3     18.17 (5.82–56.72)     18.17 (48.10)     0.24     17.97 (5.76)       Infections and infestations     Carcinoembryonic antigen increased     7     17.92 (8.50–37.75)     17.91     0.24     17.71 (8.41)       Increase     7     16.30 (7.74–34.34)     16.29 (99.2)     0.16)     10.57       Intervisities*     3     16.15 (5.18–50.38)     16.15 (42.19)     0.25     15.99 (5.13) <	Nervous system disorders					(0.07)	
Investigations     Bone lesion*     15     23.03 (13.83-38.35)     23.00     0.22     22.68       Skin and subcutaneous tissue     (311.07)     (0.13)     (13.62)       disorders     Nutritional condition abnormal     3     22.15 (7.09-69.25)     22.15 (59.72)     0.22     21.85 (6.99)       Hepatobiliary disorders	Blood and lymphatic system	Gingival erythema	3	23.98 (7.67–75.01)	23.97 (65.04)	0.22	23.62 (7.55)
Investigations   Doine teston <sup>-1</sup> 15   25.00   0.22   22.08     Skin and subcutaneous tissue   (311.07)   (0.13)   (13.62)     disorders   Nutritional condition abnormal   3   22.15 (7.09–69.25)   22.15 (59.72)   0.22   21.85 (6.99)     Hepatobiliary disorders   (0.07)   (0.10)   (0.10)   (0.10)   (0.10)     General disorders and   Diabetic coma   5   20.57 (8.51–49.71)   20.56 (91.83)   0.23   20.30 (8.40)     administration site conditions   France   (0.10)   (0.10)   (0.10)   (0.10)     Respiratory, thoracic and mediastinal disorders   Hilar lymphadenopathy   3   18.17 (5.82–56.72)   18.17 (48.10)   0.24   17.97 (5.76)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     increased   Increased   (110.47)   (0.11)   (0.16)   (10.57)     Hepatic mass   7   16.30 (7.74–34.34)   16.29 (9.45)   0.25   16.61     (0.08)   (0.12)   (0.16)   (0.17)   (0.18)   (0.18)   (0.18) <td>disorders</td> <td>Dono locion*</td> <td>15</td> <td>00.00 (10.00.00.0F)</td> <td>22.00</td> <td>(0.07)</td> <td>22.60</td>	disorders	Dono locion*	15	00.00 (10.00.00.0F)	22.00	(0.07)	22.60
John and subtriatedus inside   (13.07)   (0.10)   (13.02)     disorders   Nutritional condition abnormal   3   22.15 (7.09–69.25)   22.15 (59.72)   0.22   20.30 (8.40)     Hepatobiliary disorders   0.07)   (0.07)   (0.07)   (0.07)     General disorders and   Diabetic coma   5   20.57 (8.51–49.71)   20.56 (91.83)   0.23   20.30 (8.40)     administration site conditions   Fespiratory, thoracic and   Hilar lymphadenopathy   3   18.17 (5.82–56.72)   18.17 (48.10)   0.24   17.97 (5.76)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.97 (8.71)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     increased   Carcinoembryonic antigen   7   16.81 (10.69–26.42)   16.78   0.25   16.61     (279.02)   (0.16)   (10.57)   Hepatic mass   7   16.30 (7.74–34.34)   16.29 (9.45)   0.25   16.05 (7.18)     (0.11)   Mucosal dryness   3   16.15 (5.18–50.38)   16.15 (42.19)   0.25 <td< td=""><td>Skip and subsutaneous tissue</td><td>Bolle lesioli"</td><td>15</td><td>23.03 (13.83–38.33)</td><td>23.00</td><td>0.22</td><td>(13.62)</td></td<>	Skip and subsutaneous tissue	Bolle lesioli"	15	23.03 (13.83–38.33)	23.00	0.22	(13.62)
Hepatobiliary disorders   Diabetic coma   5   20.57 (8.51–49.71)   20.56 (91.83)   0.23   20.30 (8.40)     administration site conditions   neediastinal disorders   0.100   0.100   0.100     Respiratory, thoracic and mediastinal disorders   118.17 (5.82–56.72)   18.17 (48.10)   0.24   17.97 (5.76)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   16.78   0.25   16.61     Vieta   Skin toxicity   19   16.81 (10.69–26.42)   16.78   0.25   16.61     Vieta   Mucosal dryness   6   16.20 (7.74–34.34)   16.20 (84.72)   0.25   16.95 (7.18)     (0.11)   Vieta   Mucosal dryness   3   15.66 (5.02–48.85)   16.61 (40.76)   0.25   15	disorders	Nutritional condition abnormal	3	22,15 (7,09-69,25)	22 15 (59 72)	0.22	21.85 (6.99)
General disorders and administration site conditions   Diabetic coma   5   20.57 (8.51–49.71)   20.56 (91.83)   0.23   20.30 (8.40)     Respiratory, thoracic and mediastinal disorders   Hilar lymphadenopathy   3   18.17 (5.82–56.72)   18.17 (48.10)   0.24   17.97 (5.76)     Infections and infestations   Carcinoembryonic antigen increased   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     Skin toxicity   19   16.81 (10.69–26.42)   16.78   0.25   16.61     Hepatic mass   7   16.30 (7.74–34.34)   16.29 (99.45)   0.25   16.13 (7.66)     Mucosal dryness   6   16.21 (7.25–36.24)   16.20 (84.72)   0.25   16.05 (7.18)     Mucosal dryness   6   16.51 (5.18–50.38)   16.15 (42.19)   0.25   15.99 (5.13)     Mucosal dryness   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25   15.99 (5.13)     Mutosal dryness   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25   15.10 (5.64)     (0.08)   (0.10)   (0.10)   (0.10)   (0.10)   (0.10)     Investigations   Eosinophil count abnormal   4   15.	Hepatobiliary disorders		-			(0.07)	
administration site conditions   Hilar lymphadenopathy   3   18.17 (5.82–56.72)   18.17 (48.10)   0.24   17.97 (5.76)     mediastinal disorders   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.97 (18.41)     Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.97 (18.41)     Infections and infestations   Carcinoembryonic antigen   7   16.81 (10.69–26.42)   16.78   0.25   16.61     Kin toxicity   19   16.81 (10.69–26.42)   16.78   0.25   16.13 (7.66)     Hepatic mass   7   16.30 (7.74–34.34)   16.29 (99.45)   0.25   16.13 (7.66)     Mucosal dryness   6   16.21 (7.25–36.24)   16.20 (84.72)   0.25   16.05 (7.18)     Mucosal dryness   6   16.15 (5.18–50.38)   16.15 (4.97)   0.25   15.99 (5.13)     Mucosal dryness   3   16.15 (5.18–50.38)   16.15 (4.97)   0.25   15.99 (5.13)     Mucosal dryness   3   15.66 (5.02–48.55)   15.66 (40.76)   0.26   15.99 (5.13)     Mucosal dryness   6   15.24 (5.69–40.81)	General disorders and	Diabetic coma	5	20.57 (8.51-49.71)	20.56 (91.83)	0.23	20.30 (8.40)
Respiratory, thoracic and mediastinal disorders     Hilar lymphadenopathy     3     18.17 (5.82–56.72)     18.17 (48.10)     0.24 (0.08)     17.97 (5.76) (0.08)       Infections and infestations     Carcinoembryonic antigen increased     7     17.92 (8.50–37.75)     17.91     0.24     17.97 (5.76)       Kin toxicity     9     16.81 (10.69–26.42)     16.78     0.25     16.61       (279.02)     (0.16)     (10.57)     (10.27)     16.13 (7.66)     (0.12)       Hepatic mass     7     16.30 (7.74–34.34)     16.29 (99.45)     0.25     16.13 (7.66)       Mucosal dryness     6     16.21 (7.25–36.24)     16.15 (42.19)     0.25     15.99 (5.13)       Investigations     Allergic sinusitis*     3     16.15 (5.18–50.38)     16.15 (42.19)     0.25     15.99 (5.13)       Investigations     Colonic abscess     3     15.66 (5.02–48.85)     15.66 (40.76)     0.25     15.01 (5.64)       Metabolism and nutrition     Eosinophil count abnormal     4     15.24 (5.69–40.81)     15.24 (5.2.69)     0.26     15.10 (5.64)       Metabolism and nutrition     Diabetic ketoacidosis     67	administration site conditions					(0.10)	
mediastinal disorders     (0.08)       Infections and infestations     Carcinoembryonic antigen increased     7     17.92 (8.50–37.75)     17.91     0.24     17.71 (8.41)       increased     101.047)     (0.11)     (0.11)     (0.12)     (0.16)     (0.16)       Skin toxicity     19     16.81 (10.69–26.42)     16.78     0.25     16.61       (279.02)     (0.16)     (10.57)     (0.12)     (0.12)     (0.12)       Hepatic mass     7     16.30 (7.74–34.34)     16.29 (99.45)     0.25     16.13 (7.66)       Mucosal dryness     6     16.21 (7.25–36.24)     16.20 (84.72)     0.25     16.13 (7.66)       Mucosal dryness     3     16.15 (5.18–50.38)     16.15 (42.19)     0.25     15.99 (5.13)       Mucosal dryness     3     15.66 (5.02–48.85)     15.66 (40.76)     0.25     15.99 (5.13)       Metabolism and nutrition     Colonic abscess     3     15.66 (5.02–48.85)     15.66 (40.76)     0.26     15.99 (5.13)       Metabolism and nutrition     Eosinophil count abnormal     4     15.24 (5.69–40.81)     15.24 (52.69)     0.	Respiratory, thoracic and	Hilar lymphadenopathy	3	18.17 (5.82–56.72)	18.17 (48.10)	0.24	17.97 (5.76)
Infections and infestations   Carcinoembryonic antigen   7   17.92 (8.50–37.75)   17.91   0.24   17.71 (8.41)     increased   (110.47)   (0.11)   (0.11)   (0.11)   (0.11)     Skin toxicity   19   16.81 (10.69–26.42)   16.28   0.25   16.61     (279.02)   (0.16)   (10.57)   (1.13)   (0.12)   (0.12)     Hepatic mass   7   16.30 (7.74–34.34)   16.29 (99.45)   0.25   16.13 (7.66)     (0.12)   Mucosal dryness   6   16.21 (7.25–36.24)   16.15 (42.19)   0.25   16.05 (7.18)     Mucosal dryness   3   16.15 (5.18–50.38)   16.15 (42.19)   0.25   15.99 (5.13)     (0.08)	mediastinal disorders		_			(0.08)	
increased   (110.47)   (0.11)     Skin toxicity   19   16.81 (10.69–26.42)   16.78   0.25   16.61     (279.02)   (0.16)   (10.57)   (0.12)   (0.12)     Hepatic mass   7   16.30 (7.74–34.34)   16.29 (99.45)   0.25   16.05 (7.18)     Mucosal dryness   6   16.21 (7.25–36.24)   16.20 (84.72)   0.25   15.05 (7.18)     Allergic sinusitis*   3   16.15 (5.18–50.38)   16.15 (42.19)   0.25   15.99 (5.13)     Colonic abscess   3   15.66 (50.2–48.85)   15.66 (40.76)   0.25   15.99 (5.13)     Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   15.24 (52.69)   0.26   15.10 (5.64)     Metabolism and nutrition   0.26   15.01 (5.64)   0.25   15.10 (5.64)   0.26   15.10 (5.64)     Metabolism and nutrition   6   15.24 (5.69–40.81)   15.24 (52.69)   0.26   15.10 (5.64)     Metabolism and nutrition   16.30 (11.81–19.13)   14.95   0.26   14.82     Metabolism and nutrition   (864.35)   (0.20)   (11.64)	Infections and infestations	Carcinoembryonic antigen	7	17.92 (8.50–37.75)	17.91	0.24	17.71 (8.41)
Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   16.27 (0.26)   0.25   16.16     Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   15.24 (52.69)   0.26   15.10 (5.64)     Investigations   Diabetic ketoacidosis   67   15.03 (11.81–19.13)   14.95   0.25   16.10 (7.64)		Increased	10	16 01 (10 60 96 49)	(110.47)	(0.11)	16.61
Hepatic mass   7   16.30 (7.74–34.34)   16.29 (99.45)   0.25   16.30 (7.66)     Mucosal dryness   6   16.21 (7.25–36.24)   16.20 (84.72)   0.25   16.05 (7.18)     Mucosal dryness   6   16.15 (5.18–50.38)   16.15 (42.19)   0.25   15.99 (5.13)     Allergic sinusitis*   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25   15.99 (5.13)     Colonic abscess   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25   15.51 (4.97)     Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   15.24 (52.69)   0.26   15.10 (5.64)     Metabolism and nutrition   0iabetic ketoacidosis   67   15.03 (11.81–19.13)   14.95   0.26   14.82     Metabolism and nutrition   (864.35)   (0.20)   (11.64)   15.64   15.24   15.24   16.35   16.35		Skill toxicity	19	10.81 (10.09–20.42)	(279.02)	(0.16)	(10.57)
Intersection   Intersection <td< td=""><td></td><td>Hepatic mass</td><td>7</td><td>16.30 (7.74–34.34)</td><td>16.29 (99.45)</td><td>0.25</td><td>16.13 (7.66)</td></td<>		Hepatic mass	7	16.30 (7.74–34.34)	16.29 (99.45)	0.25	16.13 (7.66)
Mucosal dryness   6   16.21 (7.25–36.24)   16.20 (84.72)   0.25   16.05 (7.18)     Allergic sinusitis*   3   16.15 (5.18–50.38)   16.15 (42.19)   0.25   15.99 (5.13)     Colonic abscess   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25   15.51 (4.97)     Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   15.24 (52.69)   0.26   15.10 (5.64)     Metabolism and nutrition		. r				(0.12)	
Investigations   Allergic sinusitis*   3   16.15 (5.18–50.38)   16.15 (42.19)   0.25 (5.13) (0.08) (0.08)     Investigations   Colonic abscess   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25 (5.13) (0.08)     Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   15.24 (52.69)   0.26 (5.10)     Metabolism and nutrition   Intersection of the tetoacidosis   67   15.03 (11.81–19.13)   14.95   0.26 (14.82)     Metabolism and nutrition   Intersection of the tetoacidosis   67   15.03 (11.81–19.13)   14.95   0.26 (14.82)		Mucosal dryness	6	16.21 (7.25–36.24)	16.20 (84.72)	0.25	16.05 (7.18)
Allergic sinusitis*   3   16.15 (5.18–50.38)   16.15 (42.19)   0.25   15.99 (5.13)     Colonic abscess   3   15.66 (5.02–48.85)   15.66 (40.76)   0.25   15.51 (4.97)     Investigations   Eosinophil count abnormal   4   15.24 (5.69–40.81)   15.24 (52.69)   0.26   15.10 (5.64)     Metabolism and nutrition						(0.11)	
Colonic abscess     3     15.66 (5.02–48.85)     15.66 (40.76)     0.25     15.51 (4.97)       Investigations     Eosinophil count abnormal     4     15.24 (5.69–40.81)     15.24 (52.69)     0.26     15.10 (5.64)       Metabolism and nutrition		Allergic sinusitis*	3	16.15 (5.18–50.38)	16.15 (42.19)	0.25	15.99 (5.13)
Colonic abscess     3     15.66 (5.02–48.85)     15.66 (40.76)     0.25     15.51 (4.97)       Investigations     Eosinophil count abnormal     4     15.24 (5.69–40.81)     15.24 (52.69)     0.26     15.10 (5.64)       Metabolism and nutrition			2	15 (( (5 00 10 05)	15 (( ( 10 50)	(0.08)	15 51 (4.05)
Investigations     Eosinophil count abnormal     4     15.24 (5.69–40.81)     15.24 (52.69)     0.26     15.10 (5.64)       Metabolism and nutrition     0.100     0.26     14.82       Metabolism and nutrition     (864.35)     0.20     (11.64)		Colonic abscess	3	15.66 (5.02–48.85)	15.66 (40.76)	0.25	15.51 (4.97)
Interconductors     Description count abiorman     4     13.24 (3.09-40.81)     13.24 (32.09)     0.26     15.10 (3.04)       Metabolism and nutrition     0.26     14.82     0.26     14.82       Metabolism and nutrition     (864.35)     (0.20)     (11.64)	Investigations	Fosinophil court abnormal	4	15 24 (5 60 40 81)	15 24 (52 60)	0.08)	15 10 (5 64)
disorders     Diabetic ketoacidosis     67     15.03 (11.81–19.13)     14.95     0.26     14.82       Metabolism and nutrition     (864.35)     (0.20)     (11.64)	Metabolism and nutrition	Losmophin count abilornia	т	10.27 (0.07-70.01)	10.27 (02.09)	(0.10)	13.10 (3.04)
Metabolism and nutrition (864.35) (0.20) (11.64)	disorders	Diabetic ketoacidosis	67	15.03 (11.81–19.13)	14.95	0.26	14.82
	Metabolism and nutrition				(864.35)	(0.20)	(11.64)

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# Y. Lin et al.

# Table 4 (continued)

SOC	РТ	Case number(n)	ROR (95% two-sided CI)	PRR ( $\chi^2$ )	IC (IC025)	EBGM (EBGM05)
disorders	Ketoacidosis	19	14.70 (9.36–23.11)	14.68	0.26	14.56 (9.26)
Gastrointestinal disorders	Blood glucose increased	406	14.06 (12.73–15.53)	(240.03) 13.64 (4724.82)	0.27	13.53
Hepatobiliary disorders	Oral pain	58	13.69 (10.56–17.74)	(4724.82) 13.63	(0.24)	(12.25) 13.52
	Hepatic lesion	12	13.43 (7.61–23.72)	(673.09) 13.42	(0.21) 0.27	(10.43) 13.32 (7.54)
Investigations	Urine output increased	5	12.84 (5.32–30.96)	(136.79) 12.83 (54.11)	(0.15) 0.27	12.74 (5.28)
Gastrointestinal disorders	Reflux gastritis*	3	12.02 (3.86–37.44)	12.02 (30.07)	(0.11) 0.28	11.93 (3.83)
Investigations	Blood glucose abnormal	42	11.60 (8.56–15.73)	11.57	(0.09) 0.28	11.49 (8.48)
Investigations Gastrointestinal disorders	Blood chloride decreased*	3	11.40 (3.66–35.50)	(402.56) 11.40 (28.25)	(0.21) 0.29	11.32 (3.64)
Gastrointestinal disorders Metabolism and nutrition	Intra-abdominal fluid	6	11.20 (5.02–25.00)	11.19 (55.30)	(0.09) 0.29	11.12 (4.98)
disorders	collection* Dysbiosis*	3	11.16 (3.58–34.73)	11.15 (27.53)	(0.13) 0.29	11.08 (3.56)
	Food aversion	3	11.05 (3.55–34.40)	11.05 (27.22)	(0.09) 0.29	10.98 (3.53)
Reproductive system and breast	Vulvovaginal dryness	6	10.90 (4.88–24.33)	10.89 (53.53)	(0.09) 0.29	10.82 (4.85)
disorders Psychiatric disorders	Impatience*	3	10.84 (3.48–33.76)	10.84 (26.61)	(0.13) 0.29	10.77 (3.46)
Respiratory, thoracic and mediastinal disorders	Pharyngeal ulceration	3	10.55 (3.39–32.84)	10.55 (25.75)	(0.09) 0.30	10.48 (3.37)
Gastrointestinal disorders Infections and infestations	Stomatitis	131	10.46 (8.80–12.43)	10.36	(0.09) 0.30	10.30 (8.66)
Reproductive system and breast disorders	Lung abscess	4	10.36 (3.87–27.69)	(1101.61) 10.35 (33.57)	(0.25) 0.30	10.29 (3.85)
Musculoskeletal and connective tissue disorders Renal and urinary disorders General disorders and administration site conditions Gastrointestinal disorders General disorders and administration site conditions	Breast disorder	4	10.29 (3.85–27.50)	10.28 (33.30)	(0.11) 0.30	10.22 (3.82)
	Spinal deformity*	3	10.20 (3.28–31.75)	10.20 (24.73)	(0.11) 0.30	10.14 (3.26)
	Polyuria*	16	10.16 (6.21–16.61)	10.14	(0.10) 0.30	10.09 (6.17)
	Thirst	36	9.93 (7.15–13.79)	(131.05) 9.90 (286.44)	(0.18) 0.30	9.85 (7.09)
Gastrointestinal disorders Gastrointestinal disorders	Oral mucosal eruption	3	9.75 (3.13–30.35)	9.75 (23.41)	(0.22) 0.31	9.70 (3.12)
Psychiatric disorders Metabolism and nutrition	Mucosal inflammation	46	9.52 (7.12–12.73)	9.49 (347.48)	(0.10) 0.31	9.44 (7.06)
disorders Investigations	Gingival pain	12	9.51 (5.39–16.78)	9.50 (90.73)	(0.23) 0.31	9.45 (5.36)
Metabolism and nutrition disorders	Lip disorder	3	9.44 (3.03–29.36)	9.43 (22.48)	(0.17) 0.31	9.38 (3.02)
	Eating disorder*	39	9.24 (6.74–12.67)	9.22 (284.08)	(0.10) 0.31	9.17 (6.69)
	Feeding disorder*	42	9.17 (6.77–12.43)	9.15 (303.10)	(0.23) 0.31	9.10 (6.72)
	Blood glucose fluctuation	14	8.80 (5.20–14.88)	8.79 (96.13)	(0.23) 0.32	8.75 (5.17)
	Diabetic metabolic	4	8.79 (3.29–23.48)	8.78 (27.43)	(0.19) 0.32	8.74 (3.27)
Gastrointestinal disorders	decompensation Diverticulum intestinal*	5	8.77 (3.64–21.13)	8.77 (34.22)	(0.12) 0.32	8.72 (3.62)
Gastrointestinal disorders Congenital, familial and	Gastric polyps*	3	8.73 (2.81–27.15)	8.73 (20.41)	(0.13) 0.32	8.68 (2.79)
genetic disorders Nervous system disorders	Gene mutation	5	8.52 (3.54–20.52)	8.52 (33.00)	(0.10) 0.32	8.48 (3.52)
Gastrointestinal disorders Infections and infestations	Taste disorder*	63	8.40 (6.56–10.77)	8.37 (406.74)	(0.13) 0.33	8.33 (6.50)
Gastrointestinal disorders General disorders and	Cheilitis	6	8.36 (3.75–18.65)	8.36 (38.66)	(0.26) 0.33	8.32 (3.73)
administration site conditions Gastrointestinal disorders Metabolism and nutrition	Dysentery*	3	7.97 (2.56–24.77)	7.96 (18.17)	(0.15) 0.33 (0.11)	7.93 (2.55)

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Y. Lin e	et al.
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# Table 4 (continued)

SOC	РТ	Case number(n)	ROR (95% two-sided CI)	PRR ( $\chi^2$ )	IC (IC025)	EBGM (EBGM05)
disorders Psychiatric disorders Metabolism and nutrition disorder	Oral disorder	10	7.75 (4.16–14.43)	7.74 (58.44)	0.34	7.71 (4.14)
	Mucosal disorder	3	7.56 (2.43–23.52)	7.56 (17.00)	(0.18) 0.34 (0.11)	7.53 (2.42)
Gastrointestinal disorders Gastrointestinal disorders	Oral mucosal blistering	9	7.33 (3.81–14.12)	7.33 (48.95)	0.35 (0.18)	7.30 (3.79)
Skin and subcutaneous tissue disorders	Diabetes mellitus	96	7.33 (5.99–8.96)	7.28 (518.25)	0.35 (0.29)	7.25 (5.93)
	Negative thoughts	3	7.03 (2.26–21.85)	7.03 (15.43)	0.36 (0.11)	7.00 (2.25)
	Insulin resistance	3	6.87 (2.21–21.36)	6.87 (14.98)	0.36 (0.12)	6.84 (2.20)
	Oral pruritus	3	6.83 (2.20–21.24)	6.83 (14.86)	0.36 (0.12)	6.80 (2.19)
	Tongue discomfort*	8	6.72 (3.36–13.46)	6.72 (38.77)	0.36 (0.18)	6.69 (3.34)
	Rash	589	6.66 (6.13–7.24)	6.40 (2691.46)	0.37 (0.34)	6.38 (5.87)
Gastrointestinal disorders Gastrointestinal disorders	Mouth swelling	9	6.52 (3.39–12.55)	6.52 (41.86)	0.37 (0.19)	6.49 (3.37)
Gastrointestinal disorders Gastrointestinal disorders	Tongue discolouration*	4	6.28 (2.35–16.78)	6.28 (17.70)	0.38 (0.14)	6.26 (2.34)
	Aphthous ulcer	14	6.25 (3.69–10.56)	6.24 (61.37)	0.38 (0.22)	6.22 (3.68)
	Dry mouth	79	5.96 (4.77–7.43)	5.92 (322.50)	0.39 (0.31)	5.91 (4.73)
Vascular disorders Nervous system disorders	Hypovolaemic shock	5	5.69 (2.36–13.69)	5.69 (19.24)	0.40 (0.17)	5.67 (2.36)
disorders	Central nervous system lesion	13	5.68 (3.29–9.79)	5.67 (49.88)	0.40	5.66 (3.28)
Gastrointestinal disorders	Skin reaction	15	5.52 (3.32-9.16)	5.51 (55.23)	0.41 (0.24)	5.50 (3.31)
disorders		/	5.23 (2.49–11.00)	5.23 (23.89)	0.42	5.22 (2.48)
	Abnormal raeces	9	5.08 (2.64–9.77)	5.08 (29.36)	0.43	5.06 (2.63)
Mussulssheletel and compositive	Decreased appetite	230	5.07 (4.45-5.78)	5.00 (736.07)	0.43	4.99 (4.38)
tissue disorders	Chapter tolerance immediated	10	5.02 (3.07-8.21)	5.02 (51.32)	0.43	5.01 (3.00)
disorders	Glucose tolerance impaired	5	4.90 (2.03–11.78)	4.89 (15.44)	0.44 (0.18)	4.88 (2.03)
Bospirotory, thoragia and	increased	24	4.80 (3.22-7.17)	4.60 (26.07)	0.44 (0.30)	4.78 (3.20)
mediastinal disorders	Lip quelling*	9	4.09 (2.44–9.03)	4.09 (20.07)	(0.23) 0.45	4.08 (2.43)
Vascular disorders	Lip sweining	27	4.08 (3.21-0.83)	4.07 (77.79)	(0.31) 0.45	4.00 (3.20)
Investigations Gastrointestinal disorders	Betching	, 16	4.03 (2.20-9.72)	4 53 (43 84)	(0.22) 0.46	4.52 (2.26)
Gastronitestinar disorders	Weight decreased	237	4 29 (3 77-4 87)	4 22 (584 17)	(0.28)	4 22 (3 71)
	Diarrhea	544	4 28 (3 93-4 67)	4 14	(0.42)	4 13 (3 79)
Musculoskeletal and connective	Muscle atrophy*	8	4 06 (2 03-8 12)	(1306.14)	(0.45)	4 05 (2 02)
tissue disorders	Colitis	32	4.01 (2.84-5.68)	4.01 (72.03)	(0.25)	4.00 (2.82)
Gastrointestinal disorders Investigations	Blood creatining increased	32	3.08 (2.09 5.30)	3.07 (104.24)	(0.35)	3.06 (2.02)
disorders Metabolism and putrition	Pash maculo papular	17	3.96 (2.46, 6.37)	3 05 (37 40)	(0.38)	3.94 (2.45)
disorders	Dehydration	79	3.66 (2.93_4.56)	3 64 (151 13)	(0.31) 0.54	3 63 (2 01)
ากราวรุสแบบร	Liver function test increased	20	3.00 (2.93-4.30)	3 55 (26 65)	(0.43) 0.55	3 55 (2 20)
	LIVEL IUNCTION TEST INCLEASED	20	J.JU (2.2 <del>9</del> –3.32)	3.33 (30.03)	(0.35)	3.33 (2.29)

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#### Table 4 (continued)

SOC	PT	Case number(n)	ROR (95% two-sided CI)	PRR ( $\chi^2$ )	IC (IC025)	EBGM (EBGM05)
Respiratory, thoracic and	Pleural effusion*	35	3.38 (2.42-4.71)	3.37 (58.36)	0.57	3.37 (2.42)
mediastinal disorders Gastrointestinal disorders Respiratory, thoracic and	Swollen tongue*	16	3.32 (2.03–5.42)	3.31 (25.80)	(0.41) 0.58 (0.35)	3.31 (2.03)
mediastinal disorders Nervous system disorders	Pneumonitis	19	3.26 (2.08–5.11)	3.26 (29.65)	0.59 (0.37)	3.25 (2.07)
Gastrointestinal disorders Gastrointestinal disorders	Dysgeusia*	34	2.97 (2.12-4.16)	2.97 (44.30)	0.64 (0.46)	2.96 (2.12)
	Nausea	360	2.56 (2.30–2.84)	2.51 (331.37)	0.75 (0.68)	2.51 (2.26)
	Vomiting	205	2.53 (2.20–2.90)	2.50 (185.52)	0.76 (0.66)	2.50 (2.18)
General disorders and administration site conditions	Asthenia	161	2.39 (2.04–2.79)	2.37 (127.66)	0.81 (0.69)	2.37 (2.02)
General disorders and administration site conditions PIK3CA-related overgrowth	Fatigue	361	2.28 (2.06–2.54)	2.25 (253.02)	0.86 (0.77)	2.25 (2.02)
Congenital, familial and genetic	Vascular malformation	3	1365.63	1357.95	0.10	1309.49
Musculoskeletal and connective	Scoliosis	3	(430.03–4336.77) 57.70	(3922.59) 57.38	(0.03) 0.17	(412.35) 57.29
Metabolism and nutrition	Hyperglycaemia	10	(18.53–179.63) 37.80 (20.21–70.69)	(165.94) 37.11	(0.05) 0.19	(18.40) 37.07
Investigations	Glycosylated haemoglobin	6	28.60 (12.79–63.97)	(351.19) 28.29	0.21	(19.82) 28.27
General disorders and administration site conditions Gastrointestinal disorders Gastrointestinal disorders	Drug effect less than expected	3	23.02 (7.40–71.62)	(157.90) 22.89 (62.78)	(0.09) 0.22 (0.07)	(12.84) 22.88 (7.35)
	Oral pain	3	16.62 (5.34–51.72)	16.54 (43.78)	0.25	16.53 (5.31)
	Stomatitis	8	15.08 (7.50–30.32)	14.87 (103.56)	0.26 (0.13)	14.86 (7.39)
Musculoskeletal and connective tissue disorders	Limb discomfort	4	12.97 (4.85–34.68)	12.88 (43.83)	0.27 (0.10)	12.87 (4.81)
Infections and infestations Skin and subcutaneous tissue	Cellulitis*	5	12.61 (5.23–30.42)	12.50 (52.92)	0.27 (0.11)	12.50 (5.18)
disorders Psychiatric disorders	Alopecia	13	7.05 (4.07–12.22)	6.90 (65.83)	0.36 (0.21)	6.90 (3.98)
	Suicide attempt*	3	6.99 (2.25–21.75)	6.96 (15.32)	0.36 (0.11)	6.96 (2.24)
General disorders and administration site conditions	Swelling	5	5.65 (2.34–13.62)	5.60 (18.93)	0.40 (0.17)	5.60 (2.32)
Investigations	Blood glucose increased	7	5.57 (2.64–11.75)	5.51 (25.92)	0.41 (0.19)	5.51 (2.62)
Investigations Metabolism and nutrition	Weight decreased	10	4.27 (2.28–7.97)	4.20 (24.53)	0.48	4.20 (2.25)
disorders	Decreased appetite	8	4.15 (2.06–8.34)	4.10 (18.81)	0.49	4.10 (2.04)
Gastrointestinal disorders	Diarrhea	22	4.08 (2.66–6.25)	3.95 (48.98)	0.50	3.95 (2.58)
General disorders and administration site conditions	Pyrexia	11	4.00 (2.20–7.26)	3.93 (24.19)	0.51 (0.28)	3.93 (2.16)

SOC, system organ class; PT, preferred term; ROR, reporting odds ratio; CI, confidence interval; PRR, proportional reporting ratio;  $\chi^2$ , chi-information component; IC, information component; IC025, the lower limit of 95% CI of the IC; EBGM, empirical Bayesian geometric mean; EBGM05, the lower limit of 95% CI of EBGM.

reflux gastritis, diverticulum intestinal, intra-abdominal fluid collection, tongue discomfort, bacteriuria, laryngitis viral, vulvovaginal candidiasis, decreased blood chloride, hepatic coma, feeding disorder, eating disorder, parosmia, cervix disorder, rectocele, allergic sinusitis, polyuria, pleural effusion, nail cuticle fissure, onychoclasis, and lymphoedema. Previous post-marketing drug safety study for alpelisib, utilizing the World Health Organization (WHO) pharmacovigilance database, revealed several unexpected AEs similar to our study. These included lip swelling (ROR = 2.78, IC025 = 0.60), intra-abdominal fluid collection (ROR = 30.22, IC025 = 1.09), feeding disorder (ROR = 17.03, IC025 = 3.03), eating disorder (ROR = 15.11, IC025 = 2.81), polyuria (ROR = 9.50, IC025 = 1.72), pleural effusion (ROR = 7.20, IC025 = 1.90), and lymphoedema (ROR = 11.74, IC025 = 1.30) [16]. Among these, polyuria may be associated with hyperglycemia, a known AE documented by the FDA. Additionally, polyuria may also be linked to diabetes insipidus or poor renal function. Besides AEs excavated from WHO pharmacovigilance database, other AEs in our study represent unexpected findings not previously mentioned in the literature. As such, these AEs merit further validation to enhance the clinical medication safety of

alpelisib. However, there are not mechanism studies associated with these unexpected AEs and further exploration is needed.

Occurrences such as PIK3CA-activated mutation, death, disease progression, hilar lymphadenopathy, lymphatic malformation, vascular malformation, gene mutation, product distribution issue, product supply issue, and breast disorder were not initially classified as alpelisib-induced AEs. These events are more likely intertwined with the natural progression of the primary disease and supply-related issues. Notably, hilar lymphadenopathy is a frequent pattern of cancer spread, especially in primary lung malignancies [18]. Furthermore, lymphatic and vascular malformations are common clinical manifestations of PROS conditions [6]. Recognizing these distinctions is crucial for a comprehensive understanding of the patient's condition and effective treatment management.

Previous studies have established that the occurrence of adverse drug reactions is significantly influenced by gender, age, and concomitant drugs [19–21]. Therefore, we stratified patients by gender, age, and concomitant use or non-use to investigate whether newly detected disproportionate AEs in the entire study population remained disproportionate after stratification. We observed that the unexpected disproportionate AEs identified in the overall study populations continued to be disproportionate in groups of females, adults, those with concomitant drug use, and those without concomitant drug use.

PIK3CA-mutated breast cancer patients constituted the vast majority of the population we collected from the FAERS database, and breast cancer occurs more commonly in adult women [22]. Therefore, these unexpected AEs were not detected in males and juveniles, possibly due to their small sample size. We believe that further research for stratified populations is necessary due to the absence of AE incidence in the FAERS database. We found the time-to-onset of different unexpected AEs was not consistent. Due to limitation of FAERS database, we got only a small quantity of time-to-onset data. It is expected that more studies will conduct in-depth research on this aspect in the future.

Given the distinct indications for alpelisib, we stratified the populations into two groups based on their indications for further research. Comparation of the general clinical characteristics between two groups revealed significant differences in gender, age, weight, and the reporting rate of serious outcomes. Even though we can not get the accurate difference of clinical characteristics between patients with distinct indication because of the limitation of FAERS database. It is still worth noting that the occurrence of alpelisib-associated AEs may vary between patients with PIK3CA-mutated breast cancer and those with PROS, which need further study. The number of reported serious outcomes caused by AEs is notably different between patients with these distinct diseases. For example, the toll of reported adverse reactions resulting in death is higher in PIK3CA-mutated breast cancer patients compared to PROS patients. However, due to the inherent limitations of a SRS, this does not indicate that the mortality associated alpelisib is different between distinct indications. Besides, lethality is influenced by many confounding factors, such as the higher mortality rate associated with malignant tumors, different time to market as well as varied dosages, necessitating further investigation.

In our exploration of AEs associated with alpelisib specifically in PROS patients, we uncovered unexpected findings, notably suicide attempts and cellulitis. These were considered significant AEs when alpelisib was used for PROS, but were not detected in the treatment of PIK3CA-mutated breast cancer patients, according to our study and the FDA's drug label. Therefore, whether suicide attempts or cellulitis are AEs associated with alpelisib used for PIK3CA-mutated breast cancer requires further investigation through randomized clinical studies. Furthermore, compared to PROS patients, those with breast cancer taking alpelisib experienced a greater variety of AEs. This phenomenon may be attributed to the larger sample size, and further controlled experiments are needed for verification. In our additional analysis of PROS patients, we discovered suicide as a novel AE not previously mentioned in safety research on alpelisib. Suicide has been identified as an adverse reaction to multiple drugs, potentially resulting in serious consequences [23–25]. However, it cannot be ruled out that suicide attempts may arise from the progression of the disease state or anxiety about treatment and be influenced by concomitant medications. To sum up, suicide, as a serious outcome, is worthy of attention when using alpelisib for PROS and warrants further investigation. Similarly, when we analyzed PIK3CA-mutated breast cancer patients treated with alpelisib, we identified additional novel AEs. Therefore, it is meaningful to categorize patients into different study populations according to their indication for the analysis of AEs associated with alpelisib.

#### 4.1. Limitations of the study

While the benefits of conducting large-scale population studies in the real world using the FAERS database are undeniable, there were several limitations inherently associated with all pharmacovigilance databases. A number of factors need to be taken into consideration to ensure a balanced interpretation of our study's results. Firstly, the voluntary nature of the FAERS database, which underpins our study, introduces the potential for arbitrary reporting, biases, and underreporting. This variability in data quality could inevitably influence the accuracy and comprehensiveness of the results. Secondly, the absence of critical clinical details and information about the multiple drugs used in combination with alpelisib poses a challenge in controlling for confounding variables, potentially impacting the reliability of the conclusions [26]. Furthermore, due to the absence of accurate patient numbers using alpelisib, it remains impossible to calculate the true incidence rates for each identified AE.

It is crucial to acknowledge that although data mining techniques cannot compensate for the inherent limitations of a SRS, the combined utilization of the large-scale database and case reports remains an effective approach for delving into adverse drug reactions [27]. The insights gleaned from this methodology provide valuable preliminary information, offering avenues for further investigation and prospective studies. Although the findings should be interpreted with caution, they represent contributions to a broader understanding of the safety profile of alpelisib and its potential implications in clinical practice.

#### 5. Conclusion

Through a comprehensive and systematic analysis of the FAERS database, we embarked on an assessment of the post-marketing

safety profile linked to alpelisib. The AE signals we identified closely align with the information provided in the FDA's official prescribing guidelines. Notably, our study unveiled twenty-one unexpected and significant AEs, expanding upon the existing knowledge derived from pre-marketing clinical trials. When we conducted separate analyses for patients with distinct indications, we made noteworthy discoveries associated with alpelisib's safety profile. These findings are particularly valuable in addressing the limitations of pre-marketing trials and serve as a crucial resource for ensuring drug safety. To establish a definitive connection between alpelisib and these newly identified AEs, further prospective clinical trials are imperative. Our study introduces a fresh perspective to the realm of clinical safety assessments concerning alpelisib, ultimately advancing our understanding in this field.

#### Ethics approval and consent to participate

Our study is a secondary analysis of publicly available summary statistics and requires no specific ethical approval.

#### Data availability statement

All data generated or analyzed during this article are included in the published article (and in its supplementary information files).

## CRediT authorship contribution statement

Yu Lin: Writing – review & editing, Data curation, Conceptualization. Xinlei Zheng: Writing – original draft, Investigation, Formal analysis, Data curation. Yan Chen: Writing – review & editing, Writing – original draft. Qichun Nian: Writing – review & editing, Data curation. Li Lin: Writing – review & editing, Writing – original draft, Data curation. Maohua Chen: Writing – review & editing, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization.

#### Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e27529.

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