Adverse Event Reporting at ClinicalTrials.gov

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Adverse Event Reporting under FDAAA

- FDAAA Title VIII covers certain clinical trials of drugs, biologics or devices
- Summary results must be reported at the trial conclusion
- Adverse Events (AEs) must be reported as part of the summary results
  - All SAEs
  - Other AEs that occur >5% frequency within any arm
- These reporting requirements are independent of trial publication

Key Points

- AEs are reported at trial completion
- Summary information only
  - # and frequency per arm
  - No patient-level data
- Includes all AEs regardless of:
  - Attribution
  - Whether or not anticipated
- Enforcement provisions for non-compliance
- Currently have results for >2,500 studies
  - 43% have associated publication
- Structured, tabular data
  - Powerful search engine

Serious Adverse Events

Hide Serious Adverse Events

Time Frame	Reported adverse events were recorded for 30 days after the last dose of study drug for individual subjects.
Additional Description	The safety population was defined as all randomized and dosed subjects with at least one follow up safety assessment.

Reporting Groups

	Description
Cethromycin	300 mg once per day (QD) for 7 days, administered orally
Clarithromycin	250 mg twice per day (BID) for 7 days, administered orally

Serious Adverse Events

	Cethromycin	Clarithromycin
Total, serious adverse events		
# participants affected / at risk	12/260 (4.62%)	9/257 (3.50%)
Cardiac disorders		
Supraventricular tachycardia * 1		
# participants affected / at risk	0/260 (0.00%)	1/257 (0.39%)
# events	0	1
Gastrointestinal disorders		
Gastric mucosal hypertrophy * 2		
# participants affected / at risk	1/260 (0.38%)	0/257 (0.00%)
# events	1	0
Gastritis * 2		
# participants affected / at risk	1/260 (0.38%)	0/257 (0.00%)
# events	1	0
Immune system disorders		
Sarcoidosis * 2		
# participants affected / at risk	1/260 (0.38%)	0/257 (0.00%)
# events	1	0
Infections and infestations		
Pneumonia † 2		
# participants affected / at risk	2/260 (0.77%)	2/257 (0.78%)
# events	2	2

† Events were collected by systematic assessment
* Events were collected by non-systematic assessment
1 Term from vocabulary, MedDRA 8.0
2 Term from vocabulary, MedDRA (8.0)

Different Slices of the Same Data

- A Phase III, Randomized, Open-Label, Multicenter Study Comparing GW572016 [lapatinib] and Capecitabine (Xeloda) versus Capecitabine in Women with Refractory Advanced or Metastatic Breast Cancer
- GlaxoSmithKline
- Sources:
  - GSK clinical trial register
  - New England Journal of Medicine
  - Drugs @ FDA: Lapatinib label

GSK Clinical Trial Register

Timing:
AEs collected from first dose … to 30 days after last dose

Frequency:
Most frequent 10 events in each group

Attribution:
Not specified

Most Frequent Adverse Events on Therapy

Safety Results: All AEs and SAEs were collected from the first dose of study medication to 30 days after the last dose. On-therapy AEs and SAEs were defined as those reported from the first dose of study medication until the last day of study medication.

Most frequent Adverse Events On-Therapy (Most frequent 10 events in each group)	Lapatinib plus Capecitabine (N=164)	Capecitabine (N=152)
Subjects with any AE, n(%)	146 (89)	138 (91)
Diarrhea	98 (60)	60 (39)
Palmar-Plantar Erythrodysaesthesia Syndrome (PPE)	80 (49)	74 (49)
Nausea	72 (44)	64 (42)
Vomiting	43 (26)	37 (24)
Rash	45 (27)	23 (15)
Anorexia	25 (15)	30 (20)
Fatigue	29 (18)	41 (27)
Stomatitis	24 (15)	18 (12)
Abdominal pain	16 (10)	25 (16)
Mucosal inflammation	18 (11)	19 (13)
Headache	15 (9)	20 (13)
Pain in extremity	21 (13)	13 (9)
Dyspnoea	18 (11)	10 (7)
Dry skin	18 (11)	8 (5)
Dyspepsia	18 (11)	5 (3)

http://ctr.gsk.co.uk/Summary/lapatinib/studylist.asp

GSK Clinical Trial Register

Timing:
On-Therapy (first dose of study medication to last day of study medication)

Frequency:
Any (i.e., all)

Attribution: related – considered by the investigator to be related to study medication

Any Serious Adverse Events on Therapy

Safety Results: All AEs and SAEs were collected from the first dose of study medication to 30 days after the last dose. On-therapy AEs and SAEs were defined as those reported from the first dose of study medication until the last day of study medication.

Serious adverse events - On-Therapy n (%)[n considered by the investigator to be related to study medication]	Lapatinib plus Capecitabine (N=164) n (%)	Capecitabine (N=152) n (%)
Subjects with any SAEs (includes both fatal and non-fatal events), n(%)	40 (24)	36 (24)
	n (%) [n related]	n (%) [n related]
Diarrhea	11 (7) [10]	11 (7) [10]
Dehydration	4 (2) [4]	4 (3) [2]
Vomiting	3 (2) [1]	4 (3) [2]
Ejection fraction decreased	4 (2) [4]	1 (<1) [0]
Dyspnoea	2 (1) [0]	2 (1) [0]
Nausea	1 (<1) [0]	3 (2) [1]
Hypokalaemia	3 (2)[2]	1 (<1) [1]
Pyrexia	2 (1) [1]	2 (1) [1]
Anaemia	2 (1) [2]	1 (<1) [1]
Mucosal Inflammation	1 (<1) [1]	2 (1) [2]
Pulmonary embolism	2 (1) [1]	1 (<1) [1]
Erysipelas	2 (1) [0]	0
Neutropenia	1 (<1) [1]	1 (<1) [1]
Peripheral oedema	1 (<1) [0]	1 (<1) [0]
Pleural Effusion	1 (<1) [0]	1 (<1) [0]
Rash	1 (<1) [1]	1 (<1) [1]

New England Journal of Medicine

Timing:
Adverse events through November 15, 2005

Frequency:
Not specified

Attribution:
Not specified

Table 3. Adverse Events.

Event	Lapatinib plus Capecitabine (N=164)					Capecitabine Alone (N=152)					P Value*
	Grade 1	Grade 2	Grade 3	Grade 4†	Any Grade	Grade 1	Grade 2	Grade 3	Grade 4†	Any Grade	
	number of events (percent)										
Diarrhea	44 (27)	33 (20)	19 (12)	2 (1)	98 (60)	21 (14)	22 (14)	17 (11)	0	60 (39)	<0.001
Nausea	48 (29)	21 (13)	3 (2)	0	72 (44)	42 (28)	18 (12)	3 (2)	0	64 (42)‡	0.83
Vomiting	30 (18)	10 (6)	3 (2)	0	43 (26)	22 (14)	11 (7)	3 (2)	0	37 (24)‡	0.80
Stomatitis	17 (10)	7 (4)	0	0	24 (15)	12 (8)	5 (3)	1 (<1)	0	18 (12)	0.57
Abdominal pain	13 (8)	10 (6)	2 (1)	0	25 (15)	17 (11)	13 (9)	2 (1)	0	32 (21)	0.23
Constipation	14 (9)	2 (1)	0	0	16 (10)	13 (9)	3 (2)	1 (<1)	0	17 (11)	0.82
Dyspepsia	13 (8)	5 (3)	0	0	18 (11)	4 (3)	1 (<1)	0	0	5 (3)	0.014
Hand–foot syndrome	16 (10)	52 (32)	12 (7)	0	80 (49)	19 (12)	39 (26)	16 (11)	0	74 (49)	1.00
Rash	32 (20)	11 (7)	2 (1)	0	45 (27)	14 (9)	7 (5)	2 (1)	0	23 (15)	0.011
Dry skin	18 (11)	0	0	0	18 (11)	6 (4)	2 (1)	0	0	8 (5)	0.10
Fatigue	16 (10)	10 (6)	3 (2)	0	29 (18)	17 (11)	18 (12)	5 (3)	1 (<1)	41 (27)	0.06
Mucosal inflammation	11 (7)	7 (4)	0	0	18 (11)	7 (5)	9 (6)	3 (2)	0	19 (12)	0.80
Asthenia	6 (4)	4 (2)	0	0	10 (6)	7 (5)	8 (5)	3 (2)	0	18 (12)	0.11
Headache	9 (5)	6 (4)	0	0	15 (9)	13 (9)	4 (3)	1 (<1)	1 (<1)	20 (13)†	0.34
Pain in extremity	13 (8)	6 (4)	1 (<1)	0	21 (13)†	9 (6)	2 (1)	1 (<1)	0	13 (9)†	0.30
Back pain	9 (5)	6 (4)	2 (1)	0	17 (10)	5 (3)	3 (2)	1 (<1)	0	9 (6)	0.22
Anorexia	18 (11)	6 (4)	1 (<1)	0	25 (15)	21 (14)	8 (5)	1 (<1)	0	30 (20)	0.37
Dyspnea	8 (5)	5 (3)	5 (3)	0	18 (11)	4 (3)	3 (2)	3 (2)	0	10 (7)	0.24

* P values were calculated with Fisher's exact test for differences in toxicities of any grade.
† A total of 13 grade 4 adverse events occurred among 10 (6%) of the patients receiving lapatinib plus capecitabine, and 16 grade 4 adverse events occurred among 11 (7%) of the patients receiving capecitabine alone. These differences are not significant.
‡ The number includes one event with an unknown grade.

N Engl J Med 2006;355:2733-43

FDA Approved Label

Timing:
Not specified

Frequency:
Occurring in ≥ 10% of patients

Attribution:
Not specified

Table 1. Adverse Reactions Occurring in ≥10% of Patients

	TYKERB 1,250 mg/day + Capecitabine 2,000 mg/m^2/day (N = 198)			Capecitabine 2,500 mg/m^2/day (N = 191)		
Reactions	**All Grades* %**	**Grade 3 %**	**Grade 4 %**	**All Grades* %**	**Grade 3 %**	**Grade 4 %**
Gastrointestinal disorders						
Diarrhea	65	13	1	40	10	0
Nausea	44	2	0	43	2	0
Vomiting	26	2	0	21	2	0
Stomatitis	14	0	0	11	<1	0
Dyspepsia	11	<1	0	3	0	0
Skin and subcutaneous tissue disorders						
Palmar-plantar erythrodysesthesia	53	12	0	51	14	0
Rash†	28	2	0	14	1	0
Dry skin	10	0	0	6	0	0
General disorders and administrative site conditions						
Mucosal inflammation	15	0	0	12	2	0
Musculoskeletal and connective tissue disorders						
Pain in extremity	12	1	0	7	<1	0
Back pain	11	1	0	6	<1	0
Respiratory, thoracic, and mediastinal disorders						
Dyspnea	12	3	0	8	2	0
Psychiatric disorders						
Insomnia	10	<1	0	6	0	0

* National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

† Grade 3 dermatitis acneiform was reported in <1% of patients in TYKERB plus capecitabine group.

Potential for ClinicalTrials.gov

- Strengths
  - Structured data tables with search capability
  - Uniform reporting rules
  - Includes some trial data not otherwise available to the public
- Limitations
  - Scope is limited to certain drug and device trials
  - Rules govern data reporting, not data collection
  - Data only as good as what the sponsor enters