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Report on study results – Hydroxychloroquine –IMS ® Disease Analyzer Germany

"Psychosis and psychotic disorders" and "Depression and suicide/self-injury" following exposure to Hydroxychloroquine and Chloroquine

Summary Information	
Title	"Psychosis and psychotic disorders" and "Depression and suicide/self-injury" following exposure to Hydroxychloroquine and chloroquine
Version identifier of the study report	3 (updated to include data on Chloroquine)
Date of report	21 August 2020
Version identifier of the study protocol	2.0
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EU PAS register number	n.a.
Active substance	Hydroxychloroquine (HCQ), chloroquine (CQ)
Research question and objectives	1. To describe the pattern of use of HCQ and CQ. 2. To estimate the incidence rate of recorded psychiatric events as coded in primary care records whilst exposed and at any time following exposure to HCQ and CQ (psychiatric events: suicidality, self-endangering behaviour, psychosis and psychotic disorders and non-psychotic depression and other emotional disorders).
Country(-ies) of study	Germany (IMS ® Disease Analyzer Germany)
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1. Rationale and background

Hydroxychloroquine (HCQ) and chloroquine (CQ) are nationally authorised 4-aminoquinoline antimalarial agents originally developed as less toxic alternatives to quinine. Both have risen to prominence in the earlier months of 2020 as potential treatments in the current COVID-19 pandemic.

Hydroxychloroquine has a European Union reference date of 1955: although still used in the prevention and treatment of malaria, it is now more commonly used for rheumatoid arthritis, discoid and systemic lupus erythematosus, dermatological conditions caused or aggravated by sunlight, and Sjögren syndrome. In the paediatric population it can be used for juvenile idiopathic arthritis (in combination with other therapies), discoid and systemic lupus erythematosus, and prevention / treatment of malaria. Psychiatric Disorders are inconsistently recorded on SmPCs across member states, with suicidal behaviour and psychoses variously listed with frequency "rare" or "unknown", and with suicidality sometimes not listed. These side effects can occur at all ages, during acute or chronic use, and in patients with or without a history of mental illness (Gonzalez-Nieto et al, 2015; Pinho de Oliveira et al, 2013), (Juurlink et al, 2020). However, the labelling of such effects is inconsistent.

Chloroquine has a European Union reference date of 1947 and remains widely used in the prophylaxis and treatment of malaria. Other licenced indications are: amoebic hepatitis, lupus erythematosus and rheumatoid arthritis. Established psychiatric disorders are hallucinations (frequency "rare"), and psychotic disorder (including anxiety, personality change); insomnia; confusion and depression (frequency "unknown").

In May 2020, the Spanish regulatory Agency (AEMPS) warned about the occurrence of neuropsychiatric reactions associated with intake of HCQ and CQ in patients being treated for COVID-19. This new information let to initiation of a signal procedure at the European Union's Pharmacovigilance Risk Assessment Committee (PRAC) and led to further review of data pertaining to the association of neuropsychiatric reactions with chloroquine/hydroxychloroquine.

Analyses of healthcare records held at the EMA could support further analyses of data relating to this signal. Such analyses would allow estimation of incidence rates for events among patients initiating treatment and patients on chronic therapy (to evaluate whether risk might be highest at the beginning of treatment) and could determine whether there is an increased risk of events in patients with neuropsychiatric history.

To help contextualization of results, a comparison of the risk of events with treatments used for similar indications would be helpful. In view of the difficulties in selecting appropriate comparators and the imminent publication of findings from the OHDSI community also studying neuropsychiatric events following exposure to HCQ (Prieto-Alhambra et al, 2020, see also entry in EU PAS database: http://www.encepp.eu/encepp/viewResource.htm?id=36203) this study will not, at present, proceed with a comparator-based analysis.

This study has considered data recorded in the electronic electronic health records database: IMS ® Disease Analyzer Germany (IMS-Germany) This database is contractually available to the EMA in-house.

2. Research Question and Objectives

The study has the following objectives for each database:

1. To describe the pattern of use of HCQ and CQ.
2. To estimate the incidence rate of recorded events as coded in primary care records whilst exposed and at any time following exposure to HCQ and CQ.

a. Suicidality
b. Self-endangering behaviour (including self-harm)
c. Affective, Psychosis and psychotic disorders
    i. Schizophrenia-like, including hallucinations
    ii. Affective related (mania, bipolar, psychotic depression)
d. Non-psychotic depression and other emotional disorders, including violent behaviour and aggression.

3. Methods

3.1. Data Sources

IMS ® Disease Analyzer Germany collects anonymized electronic health records (EHRs) through a representative panel of GPs, some specialists in internal medicine, and other specialist physicians (~ 3% of all GPs in Germany), stratified for specialist group, region, community size, and age of physician. In Germany, patients can visit a physician of choice, including specialist physicians in gynaecology, dermatology and paediatric, whenever a medical need emerges.

3.2. Study design

This is a cohort study with cohorts defined based on patients' exposure to the medicines under investigation. Descriptive analyses are used to describe the pattern of use of HCQ and CQ. The occurrence of events in the exposed population are described as unadjusted event rates. Analyses require the use of a minimum one-year lookback period prior to the start of follow-up to establish any baseline characteristics and a new-user "inception" cohort of patients established through the one-year screening period to define incident use. In an "ever used" analysis (akin to "intention to treat"), Patients are followed from the date of first prescription until an event or censored (at the end of follow-up). In an "on treatment" analysis, patients are followed for the duration of their therapy.

3.3. Study population

The population eligible for the study consists of all patients in IMS ® Disease Analyzer Germany with an observation period of one-year or more at the time of their first prescription for HCQ or CQ. Patients are followed until their last consultation, or, in case of interruptions in consultation lasting 366 days or longer, follow-up will end on day 365 after the consultation immediately prior to the interruption. The study subjects are followed from the first use of HCQ and QC on the database (1992 onwards) to most recent data available (December 2019). In any case data do not cover data collected from the ongoing COVID-19 pandemic.

3.4. Study variables

3.4.1. Drug Exposures

Patients included are those exposed to HCQ (ATC code P01BA02) or QC (P01BA01).

3.4.2. Outcomes

The following serious neuropsychiatric outcomes are defined as follows:

- **Suicidality** (events where the medical event text indicates possible suicidality)
- **Self-endangering behaviour** (including self-harm)

- **Psychosis and psychotic disorders**: to include: (i) schizophrenia-like including hallucinations and (ii) associated affective disorders (mania, bipolar disease, psychotic depression).
- **Non-psychotic depression and other emotional disorders:** including violent behaviour and aggression

A composite of self-endangering behaviour and suicidality has been included as an additional endpoint.

3.5. Data Analysis

Analyses were conducted using SAS v9.4.

The analyses followed the objectives and were run in the databases indicated. All of the analyses in the study were performed by the authors based on data available in IMS® Disease Analyzer Germany.

3.5.1. Pattern of use

Descriptive analyses were used to describe and summarise the study cohorts (HCQ and CQ) at baseline: this includes the number of patients exposed, age at first use, sex, year of first use and numbers of prescriptions and exposure windows per patient. This also describes indication, the proportion of patients with previous neuropsychiatric diagnoses, and dose of HCQ and CQ. The cumulative dose of HCQ at the time of event has been summarised.

3.5.2. Incidence rates [HCQ only]

The initial analysis follows up from first use to event, end of treatment exposure or censoring. Incidence rates were calculated as the number of events occurring during follow-up divided by the person years of follow-up with 95% confidence intervals. As provided in the pilot analysis, these are broken down by) age & sex, dose (high dose vs low dose) and history of neuropsychiatric diagnoses, and (in addition) by indication. The time from exposure to onset of event is described using Kaplan-Meier survival curves: these were also broken down by age & sex, dose, history of neuropsychiatric diagnoses, and indication for the initial episode of exposure only.

4. Limitations

IMS ® Disease Analyzer Germany has limited recording of suicidal events and self-harm events and is not expected to contribute significantly to the assessment of these events. Analysis of the other outcomes has been possible. Other approaches to the analysis were considered, for example using a self-controlled type design; however, such analysis relies on clear treatment windows with well-defined periods of "time on" and "time off" therapy: due to the excessively slow elimination of HCQ and QC from the body and the expected chronicity of treatment, and the possibility for incomplete data, such an approach was not considered feasible.

In Germany the patient has free physician choice: in epidemiologic studies patients can only be followed for as long as they continue to visit the same physician as patients are not identifiable across physician practices for confidentiality reasons. Furthermore, as the patient can visit several physicians concurrently, collected data may be incomplete.

The data describing CQ exposure is flawed as much exposure dated from before 2004 when there are concerns about data quality. This is described in further detail in section 7.2.

5. Ethical / data protection considerations

This work uses de-identified data provided by patients as a part of their routine primary care. Only aggregate data are presented.

6. Publication of study results

This study will be registered in the EU PAS Register. After finalisation of analyses, the protocol as well as the study results will be published in the EU PAS Register.

7. Results

7.1. Hydroxychloroquine

7.1.1. Pattern of use: HCQ

Descriptive analyses were performed to describe and summarise the study cohorts (HCQ) at baseline: this includes the number of patients exposed, age at first use, sex, year of first use and numbers of prescriptions and exposure windows per patient. This describes indication, the proportion of patients with previous neuropsychiatric diagnoses, and dose of HCQ. The cumulative dose of HCQ at the time of event has been summarised.

Table 1.1 Patient demographic summary

	Hydroxychloroquine
Total no of patients [1]	8710
No. of female patients (%)	7106 (81.6%)
Mean age in years (SD)	56.1 (15.5)
Median age (IQR)	57.0 (46.0-68.0)
Min- max age	2-95
No. with missing age information	13
Start year before 2000	171
Start year 2000-2004	323
Start year 2005-2009	1541
Start year 2010-2014	2791
Start year 2015-2019	3884

[1] Four patients had never a diagnosis recorded and have been excluded from the analyses below.

Table 2.1. Prescriptions, doses (in mg) and treatment episodes

	Hydroxychloroquine
Total no. of patients	8706
Total no. of episodes	11,159
Min-max episodes	1-9
Mean episodes (SD)	1.28 (0.74)
Median episodes (IQR)	1.00 (1.00 -1.00)
Total no. of prescription dates	51,632
Min-max prescription dates	1-125
Mean prescription dates (SD)	5.93 (9.43)
Median prescription dates (IQR)	2.00 (1.00-6.00)
No. of patients with calculated start dose (calculated dose during first treatment episode)	8683
Min-max calculated start dose in mg	90-700
Mean calculated start dose (SD) in mg	237.1 (61.6)
Median calculated start dose (IQR) in mg [1]	240.0 (190.0-270.0)
No. of patients with a calculated start dose up to 100 mg	19 (0.2%)
No. of patients with a calculated start dose between 101-200 mg	2795 (32.1%)
No. of patients with a calculated start dose between 201-300 mg	4847 (55.7%)
No. of patients with a calculated start dose between 301-400 mg	918 (10.5%)
No. of patients with a calculated start dose between 401-500 mg	81 (0.9%)
No. of patients with a calculated start dose greater than 500 mg	23 (0.3%)

[1] The median start dose was selected in the stratification by dose analysis.

Table 3.1. Indications

	Hydroxychloroquine
Total no of patients with any prior diagnosis [1]	8671 (99.6%)
No of patients with no prior diagnosis	35 (0.4%)
No of patients with RA	4422 (50.8%)
No of patients with juvenile RA	104 (1.2%)
No of patients with lupus	1040 (11.9%)
No of patients with systemic lupus	795 (9.1%)
No of patients with other diagnoses and none of the above diagnoses	2828 (32.5%) [2]

[1] Diagnoses for which the diagnosis certainty was provided as 'exclusion of', which indicated that the patient did not have the diagnosis, have been excluded.
[2] Diagnoses include e.g. unspecified systemic connective tissue disease (ICD 10 code M35.9; n=493), unspecified rheumatism (ICD 10 code M79.0; n=409), sicca syndrome (ICD 10 code M35.0; n=310) and unspecified polyarthrosis (ICD 10 code M15.9; n=251).

RA = rheumatoid arthritis. Please note that diagnosis categories are not mutually exclusive.

Table 4.1. Prior neuropsychiatric diseases

	Hydroxychloroquine
All patients	8706 (100%)
No of patients with any prior neuropsychiatric diagnosis	1539 (17.7%)
No of patients with prior suicidal events	8 (0.1%)
No of patients with prior self-harm events	4 (0.0%)
No of patients with schizophrenia psychosis related events	48 (0.6%)
No of patients with affective psychosis related events	37 (0.4%)
No of patients with non-psychotic affective disorders	1521 (17.5%)

Table 5. Cumulative dose of HCQ at the time of event [1]

Drug	Hydroxychloroquine
n patient with exposed event	675
n exposed patients with calculated cumulative dose	673 [2]
mean cumulative dose	96,369 mg
median cumulative dose	28,350 mg
minimum, maximum	190 mg - 1,509,160 mg

[1] All neuropsychiatric events during the first treatment episode have been included. The cumulative dose concerns the dose at the time of the first recorded neuropsychiatric event.
[2] In two patients the cumulative dose could not be calculated due to not being able to assign a daily dose.

Incidence rates: HCQ

The initial analysis follows up from first use to event or end of treatment exposure/censoring. Incidence rates are calculated as the number of events during treatment exposure and during the entire follow-up period divided by the person years of follow-up with 95% confidence intervals. These are broken down by type of treatment (HCQ), age & sex, dose (high dose vs low dose based on median dose) and history of neuropsychiatric diagnoses, and (in addition) by indication.

The time from exposure to onset of event will be described for events occurring during the first treatment episode using Kaplan-Meier survival curves: these are also broken down by age & sex, dose, history of neuropsychiatric diagnoses, and indication. As the same patient may have more than one indication, for the purpose of stratifying Kaplan-Meier survival curves by indication, the following order of preference was applied: Juvenile rheumatoid arthritis>rheumatoid arthritis>systemic lupus erythematosis>lupus erythematosis.

These analyses are based on the December 2019 version of the database whereas pilot data were based on the June 2019 version. Also, these analyses use a slightly broader definition of self-harm, including also include cases without a medical event text for the ICD 10 code Z91.5 (personal history of self-harm) as self-harm.

Table 6. History of neuropsychiatric diagnoses: HCQ

Incident HCQ exposure [1]	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)					any follow-up time	*n* any time vents event rate (95% CI)				
			suicidality	self-endangering	suicidality or self-endangering	psychosis related	non-psychotic depression		suicidality	self-endangering	suicidality or self-endangering	psychosis related	non-psychotic depression
no neuropsychiatric history	7167	11,045	1 0.91 (0.02-5.05)	0 0.0	1 0.91 (0.02-5.05)	13 11.8 (6.27-20.1)	288 260.7 (231.5-292.7)	26,404	5 1.89 (0.61-4.42)	2 0.76 (0.09-2.74)	5 1.89 (0.61-4.42)	31 11.7 (8.0-16.7)	619 234.4 (216.3-253.6)
suicidality	8	19	0 0.0	0 0.0	0 0.0	0 0.0	5 2589 (840.5-6041)	32	0 0.0	0 0.0	0 0.0	0 0.0	6 1879 (689.6-4090)
self-endangering behaviour	4	7	0 0.0	0 0.0	0 0.0	0 0.0	2 2751 (333.1-9936)	12	0 0.0	0 0.0	0 0.0	0 0.0	2 1703 (206.2-6151)
Psychosis and psychotic disorders	83	112	1 88.9 (2.25-495.3)	0 0.0	1 88.9 (2.25-495.3)	11 977.8 (488.1-1750)	22 1956 (1226-2961)	277	2 72.3 (8.76-261.2)	1 36.2 (0.92-201.5)	2 72.3 (8.76-261.2)	19 687 (413.6-1073)	34 1229 (851.4-1718)
Non-psychotic depression and other emotional disorders	1521	2391	2 8.36 (1.01-30.2)	1 4.18 (0.11-23.3)	3 12.5 (2.59-36.7)	13 54.4 (29.0-93.0)	453 1894 (1724-2077)	6233	7 11.2 (4.52-23.1)	4 6.42 (1.75-16.4)	8 12.8 (5.54-25.3)	37 59.4 (41.8-81.8)	688 1104 (1023-1189)

Table 7. Age & sex distribution in patients taking HCQ

Incident HCQ exposure	sex	age (years)	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
					suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	female	< 18	71	103	1 97.4 (2.47-542.5)	0 0.0	1 97.4 (2.47-542.5)	2 194.7 (23.6-703.4)	230	1 43.5 (1.10-242.5)	0 0.0	1 43.5 (1.10-242.5)	2 87.0 (10.5-314.4)
		18-50	2237	3656	1 2.74 (0.07-15.2)	1 2.74 (0.07-15.2)	7 19.1 (7.70-39.5)	179 489.7 (420.6-566.9)	8551	5 5.85 (1.90-13.7)	3 3.51 (0.72-10.3)	20 23.4 (14.3-36.1)	325 380.1 (339.9-423.7)
		50-70	3426	5541	0 0.0	0 0.0	12 21.7 (11.2-37.8)	316 570.3 (509.2-636.8)	13,541	3 2.22 (0.46-6.48)	2 1.48 (0.18-5.34)	21 15.5 (9.60-23.7)	537 396.6 (363.7-431.6)
		>70	1356	1792	0 0.0	0 0.0	5 27.9 (9.06-65.1)	133 742.2 (621.4-879.6)	4309	1 2.32 (0.06-12.9)	1 2.32 (0.06-12.9)	18 41.8 (24.8-66.0)	226 524.4 (458.3-597.5)
	male	< 18	22	30	0 0.0	0 0.0	0 0.0	1 338.8 (8.58-1888)	56	0 0.0	0 0.0	0 0.0	1 179.1 (4.54-998.0)
		18-50	395	609	1 16.4 (0.42-91.4)	0 0.0	2 32.8 (3.97-118.5)	32 525.1 (359.2-741.3)	1569	1 6.37 (0.16-35.5)	0 0.0	5 31.9 (10.3-74.4)	65 414.2 (319.6-527.9)
		50-70	827	1239	0 0.0	0 0.0	2 16.1 (1.96-58.3)	56 452.0 (341.4-587.0)	3263	0 0.0	0 0.0	7 21.5 (8.63-44.2)	108 331.0 (271.5-399.6)
		>70	359	460	0 0.0	0 0.0	1 21.7 (0.55-121.1)	20 434.6 (265.5-671.2)	1135	1 8.81 (0.22-49.1)	0 0.0	1 8.81 (0.22-49.1)	43 378.9 (274.2-510.4)
with neuro-psychiatric history	female	< 18	6	8	1 1209 (30.6-6736)	0 0.0	1 1209 (30.6-6736)	1 1209 (30.6-6736)	16	1 638.8 (16.2-3559)	0 0.0	1 638.8 (16.2-3559)	1 638.8 (16.2-3559)
		18-50	351	522	1 19.2 (0.49-106.7)	1 19.2 (0.49-106.7)	3 57.5 (11.9-167.9)	105 2011 (1645-2435)	1497	3 20.0 (4.13-58.6)	3 20.0 (4.13-58.6)	12 80.1 (41.4-140.0)	165 1102 (940.3-1284)
		50-70	713	1243	0 0.0	0 0.0	8 64.4 (27.8-126.8)	208 1674 (1454-1917)	3054	2 6.55 (0.79-23.7)	1 3.27 (0.08-18.3)	12 39.3 (20.3-68.7)	308 1009 (899.2-1128)
		>70	252	339	0 0.0	0 0.0	2 59.0 (7.15-213.3)	76 2244 (1768-2808)	859	0 0.0	0 0.0	9 104.8 (47.9-198.9)	117 1362 (1127-1632)
	male	< 18	0	0	NA	NA	NA	NA	0	NA	NA	NA	NA
		18-50	51	71	0 0.0	0 0.0	2 281.8 (34.1-1018)	18 2536 (1503-4008)	226	0 0.0	0 0.0	4 176.7 (48.1-452.3)	27 1193 (785.9-1735)
		50-70	116	165	0 0.0	0 0.0	1 60.8 (1.54-338.6)	33 2005 (1380-2816)	460	0 0.0	0 0.0	4 86.9 (23.7-222.6)	51 1109 (825.4-1458)
		>70	46	58	0 0.0	0 0.0	0 0.0	11 1882 (939.4-3367)	159	1 62.8 (1.59-349.8)	0 0.0	0 0.0	20 1256 (767.0-1939)
no neuro-psychiatric history	female	< 18	65	94	0 0.0	0 0.0	0 0.0	1 105.9 (2.68-590.0)	214	0 0.0	0 0.0	0 0.0	1 46.7 (1.18-260.2)
		18-50	1886	3133	0 0.0	0 0.0	4 12.8 (3.48-32.7)	74 236.2 (185.4-296.5)	7053	2 2.84 (0.34-10.2)	0 0.0	8 11.3 (4.90-22.4)	160 226.8 (193.1-264.8)
		50-70	2713	4298	0 0.0	0 0.0	4 9.31 (2.54-23.8)	108 251.3 (206.1-303.4)	10487	1 0.95 (0.02-5.31)	1 0.95 (0.02-5.31)	9 8.58 (3.92-16.3)	229 218.4 (191.0-248.6)
		>70	1104	1453	0 0.0	0 0.0	3 20.6 (4.26-60.3	57 392.2 (297.1-508.2)	3450	1 2.90 (0.07-16.2)	1 2.90 (0.07-16.2	9 26.1 (11.9-49.5)	109 315.9 (259.4-381.1)
	male	< 18	22	30	0 0.0	0 0.0	0 0.0	1 338.8 (8.58-1888)	56	0 0.0	0 0.0	0 0.0	1 179.1 (4.54-998.0)
		18-50	344	538	1 18.6 (0.47-103.5	0 0.0	0 0.0	14 260.0 (142.1-436.2)	1343	1 7.45 (0.19-41.5)	0 0.0	1 7.45 (0.19-41.5)	38 282.9 (200.2-388.4)
		50-70	711	1074	0 0.0	0 0.0	1 9.31 (0.24-51.9)	23 214.1 (135.7-321.2)	2803	0 0.0	0 0.0	3 10.7 (2.21-31.3)	57 203.4 (154.0-263.5)
		>70	313	402	0 0.0	0 0.0	1 24.9 (0.63-138.7)	9 224.0 (102.4-425.3)	976	0 0.0	0 0.0	1 10.3 (0.26-57.1)	23 235.8 (149.5-353.8)

NA = not applicable.

Table 8. Dose (high dose vs low dose) in patients taking HCQ

Incident HCQ exposure [1]	daily dose (mg)	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	≤240	5360	8434	1 1.19 (0.03-6.61)	1 1.19 (0.03-6.61)	17 20.2 (11.7-32.3)	412 488.5 (442.5-538.0)	19,423	5 2.57 (0.84-6.01)	4 2.06 (0.56-5.27)	42 21.56 (15.6-29.2)	718 369.7 (343.1-397.7)
	>240	3323	4953	2 4.04 (0.49-14.6)	0 0.0	13 26.2 (14.0-44.9)	326 658.1 (588.6-733.6)	13,189	7 5.31 (2.13-10.9)	2 1.52 (0.18-5.48)	31 23.5 (16.0-33.4)	588 445.8 (410.5-483.4)
with neuropsychiatric history	≤240	894	1398	1 7.15 (0.18-39.9)	1 7.15 (0.18-39.9)	8 57.2 (24.7-112.8)	246 1760 (1547-1994)	3525	4 11.3 (3.09-29.1)	4 11.3 (3.09-29.1)	22 62.4 (39.1-94.5)	381 1081 (975.1-1195)
	>240	640	994	1 10.1 (0.25-56.0)	0 0.0	9 90.5 (41.4-171.8)	206 2072 (1798-2375)	2732	3 11.0 (2.26-32.1)	0 0.0	20 73.2 (44.7-113.0)	308 1127 (1005-1260)
no neuropsychiatric history	≤240	4466	7036	0 0.0	0 0.0	9 12.8 (5.85-24.3)	166 235.9 (201.4-274.7)	15,898	1 0.63 (0.02-3.51)	0 0.0	20 12.6 (7.69-19.4)	337 212.0 (189.9-235.9)
	>240	2683	3959	1 2.53 (0.06-14.1)	0 0.0	4 10.1 (2.75-25.9)	120 303.1 (251.3-362.4)	10,456	4 3.83 (1.04-9.79)	2 1.91 (0.23-6.91)	11 10.5 (5.25-18.8)	280 267.8 (237.3-301.0)

Table 9. Recorded indications in patients with HCQ

Incident HCQ exposure [1]	indication	n patients	exposed years follow-up	*n* exposed events event rate (95% CI)				any follow-up time	*n* any time vents event rate (95% CI)			
				suicidality	self-harm	psychosis related	non-psychotic depression		suicidality	self-harm	psychosis related	non-psychotic depression
all	RA	4422	6791	0 0.0	1 1.47 (0.04-8.20)	13 19.1 (10.2-32.7)	383 564.0 (508.9-623.3)	17,411	3 1.72 (0.36-5.04)	3 1.72 (0.36-5.04)	30 17.2 (11.6-24.6)	669 384.3 (355.7-414.5)
	juvenile RA	104	127	1 78.7 (1.99-438.3)	0 0.0	1 78.7 (1.99-438.3)	6 472.0 (173.2-1027)	270	1 37.0 (0.94-206.1)	0 0.0	1 37.0 (0.94-206.1	8 295.8 (127.7-582.9)
	lupus	1040	1769	3 17.0 (3.50-49.6)	0 0.0	3 17.0 (3.50-49.6)	108 610.4 (500.7-736.9)	3511	5 14.2 (4.62-33.2	1 2.85 (0.07-15.9)	7 19.9 (8.02-41.1)	167 475.7 (406.3-553.5)
	systemic lupus	795	1617	0 0.0	0 0.0	5 30.9 (10.0-72.1)	71 439.0 (342.8-553.7)	2906	0 0.0	0 0.0	5 17.2 (5.59-40.2)	115 395.7 (326.7-474.9)
	other	2828	4033	0 0.0	0 0.0	10 24.8 (11.9-45.6)	240 595.1 (522.2-675.3)	10,260	4 3.90 (1.06-9.98)	2 1.95 (0.24-7.04)	34 33.1 (23.0-46.3)	455 443.5 (403.6-486.2)
with neuropsychiatric history	RA	785	1250	0 0.0	1 8.00 (0.20-44.6)	8 64.0 (27.6-126.1)	232 1855 (1624-2110)	3268	1 3.06 (0.08-17.1)	1 3.06 (0.08-17.1)	19 58.1 (35.0-90.8	359 1098 (987.7-1218)
	juvenile RA	12	11	1 941.2 (23.8-5244)	0 0.0	1 941.2 (23.8-5244)	3 2824 (582.3-8252)	23	1 440.2 (11.2-2453)	0 0.0	1 440.2 (11.2-2453)	3 1321 (272.3-3859)
	lupus	210	368	2 54.3 (6.58-196.2)	0 0.0	2 54.3 6.58-196.2)	61 1657 (1267-2128)	801	4 49.9 (13.6-127.9)	1 12.5 (0.32-69.6)	5 62.4 (20.3-145.7)	88 1099 (881.3-1354)
	systemic lupus	143	280	0 0.0	0 0.0	1 35.7 (0.91-199.1)	36 1287 (901.1-1781)	568	0 0.0	0 0.0	1 17.6 (0.45-98.1)	54 950.7 (714.2-1240)
	other	526	727	0 0.0	0 0.0	6 82.6 (30.3-179.7)	158 2174 (1848-2541)	2110	2 9.48 (1.15-34.3)	2 9.48 (1.15-34.3)	19 90.1 (54.2-140.6)	245 1161 (1020-1316)
no neuropsychiatric history	RA	3637	5541	0 0.0	0 0.0	5 9.02 (2.93-21.1)	151 272.5 (53.1-752.6)	14,142	2 1.41 (0.17-5.11)	2 1.41 (0.17-5.11)	11 7.78 (3.88-13.9)	310 219.2 (195.5-245.0)
	juvenile RA	92	116	0 0.0	0 0.0	0 0.0	3 257.5 (53.1-752.6)	248	0 0.0	0 0.0	0 0.0	5 201.9 (65.5-471.1)
	lupus	830	1401	1 7.14 (0.18-39.8)	0 0.0	1 7.14 (0.18-39.8)	47 335.4 (246.5-446.0)	2710	1 3.69 (0.09-20.6)	0 0.0	2 7.38 (0.89-26.7)	79 291.5 (230.8-263.3)
	systemic lupus	652	1338	0 0.0	0 0.0	4 29.9 (8.15-76.6)	35 261.7 (182.3-363.9)	2338	0 0.0	0 0.0	4 17.1 (4.66-43.8)	61 260.9 (199.5-335.1)
	other	2302	3306	0 0.0	0 0.0	4 12.1 (3.300-31.0)	82 248.0 (197.3-307.8)	8150	2 2.45 (0.30-8.87)	0 0.0	15 18.4 (10.3-30.4)	210 257.7 (224.0-295.0)

Figure 1. Kaplan Meier survival curves showing time-to-event for neuropsychiatric events during first treatment episode following first exposure: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-730 days), then the 0-4200 days period of the large graph).

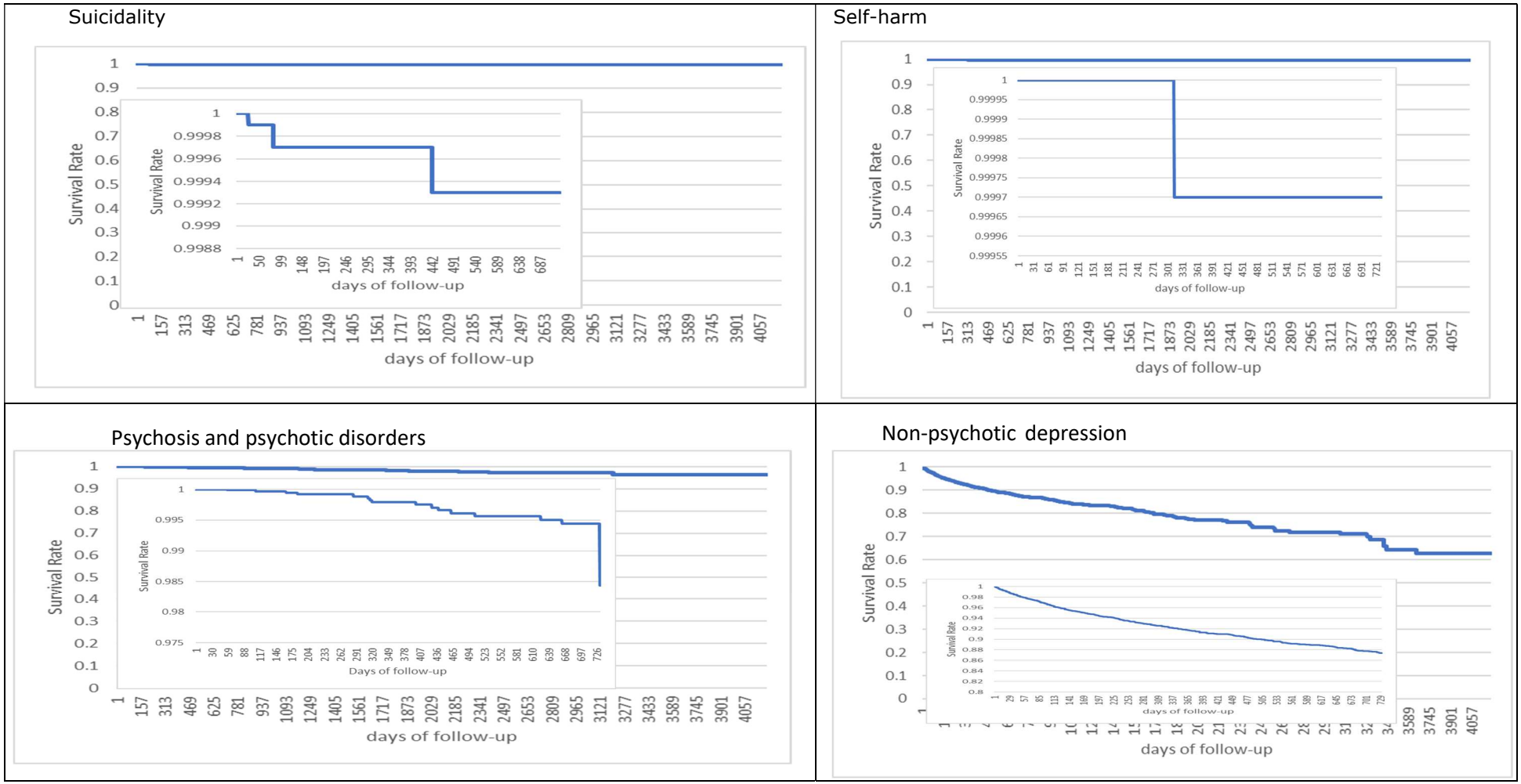


Figure 2. Kaplan Meier survival curves stratified by age: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-730 days), then the 0-4200 days period of the large graph).

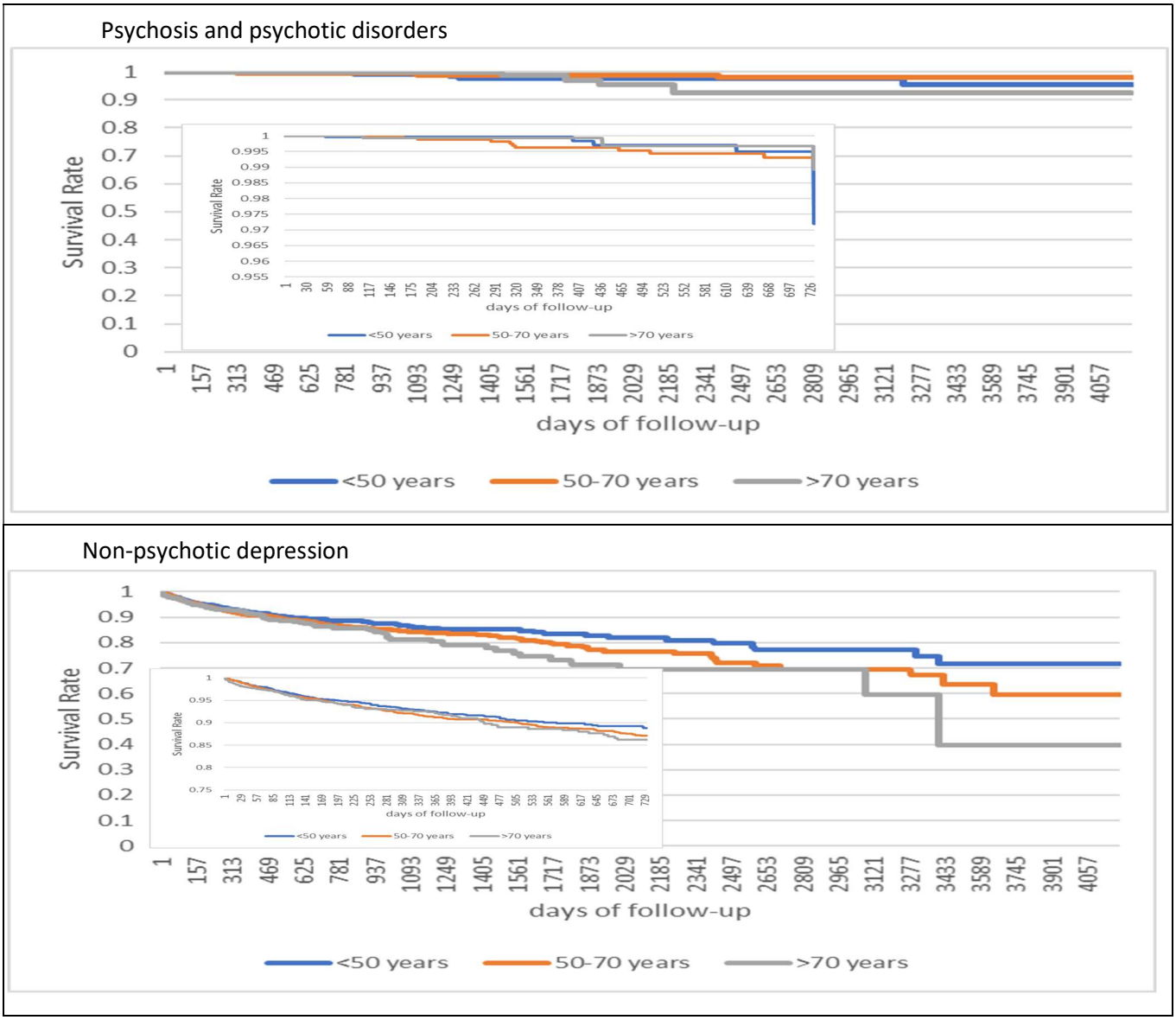


Figure 3. Kaplan Meier survival curves stratified by sex: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-730 days), then the 0-4200 days period of the large graph).

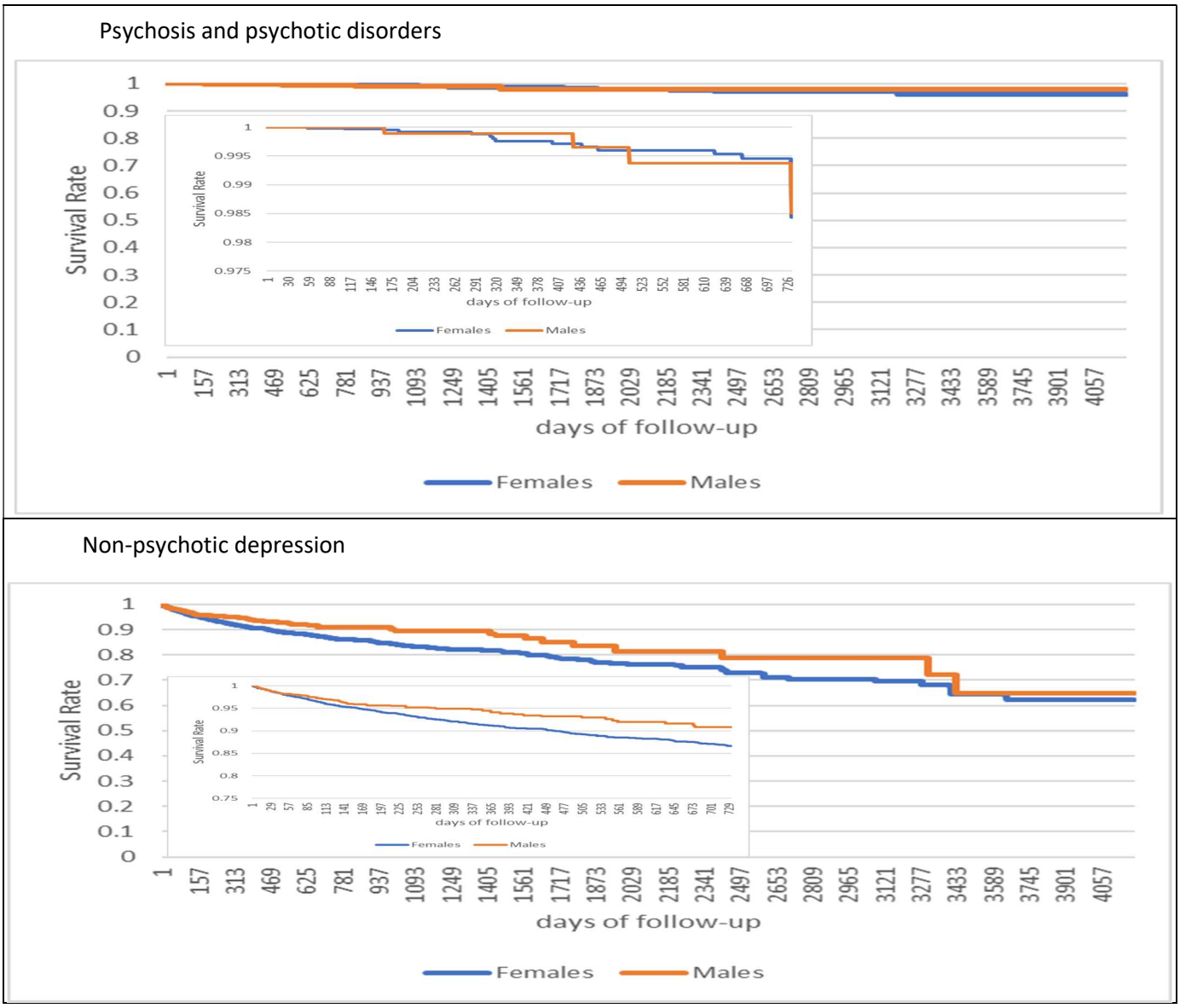


Figure 4. Kaplan Meier survival curves stratified by dose (Low dose ≤240 mg, High dose >240mg): HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-730 days), then the 0-4200 days period of the large graph).

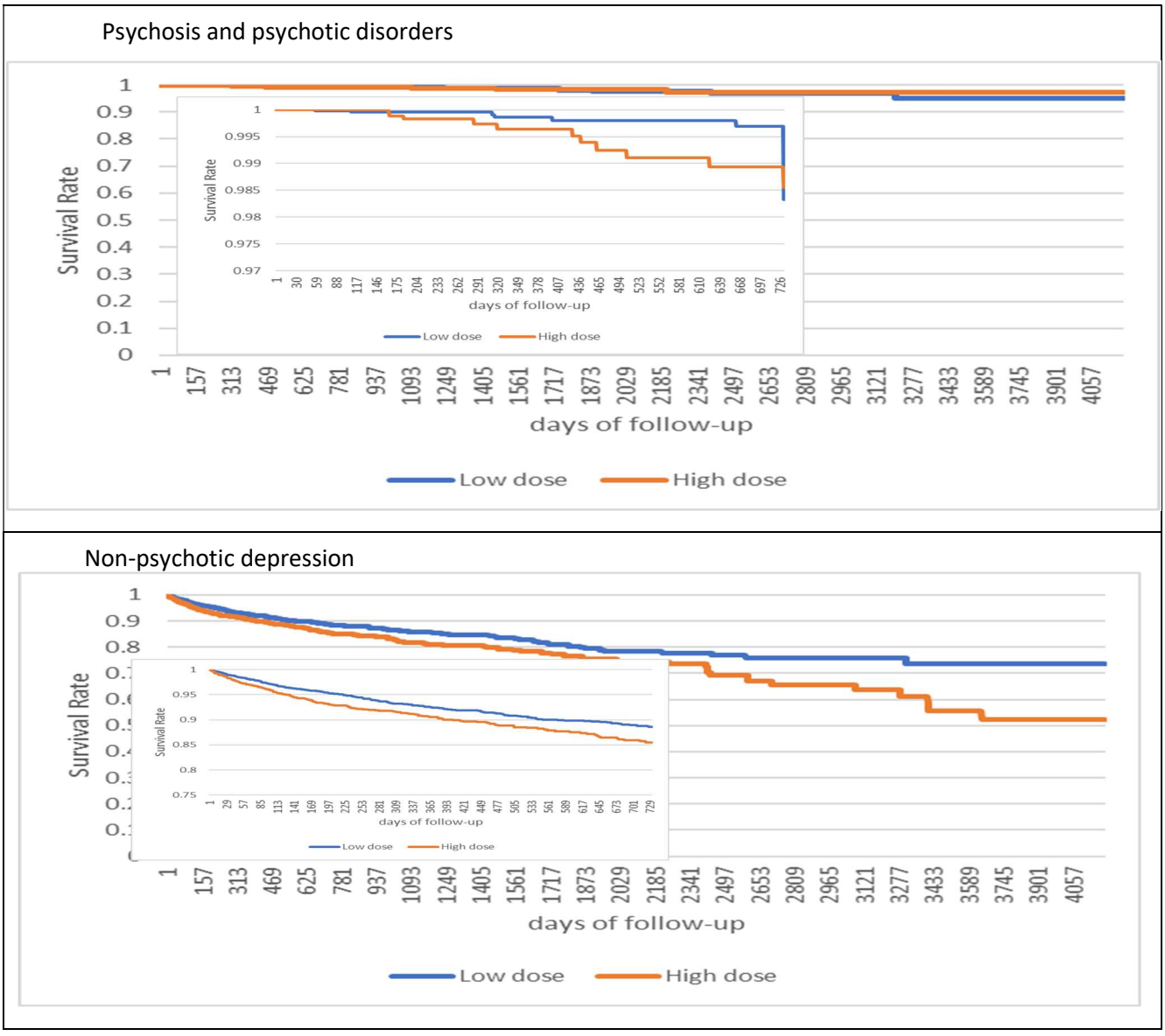


Figure 5. Kaplan Meier survival curves stratified by history of neuropsychiatric diagnoses: HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-730 days), then the 0-4200 days period of the large graph).

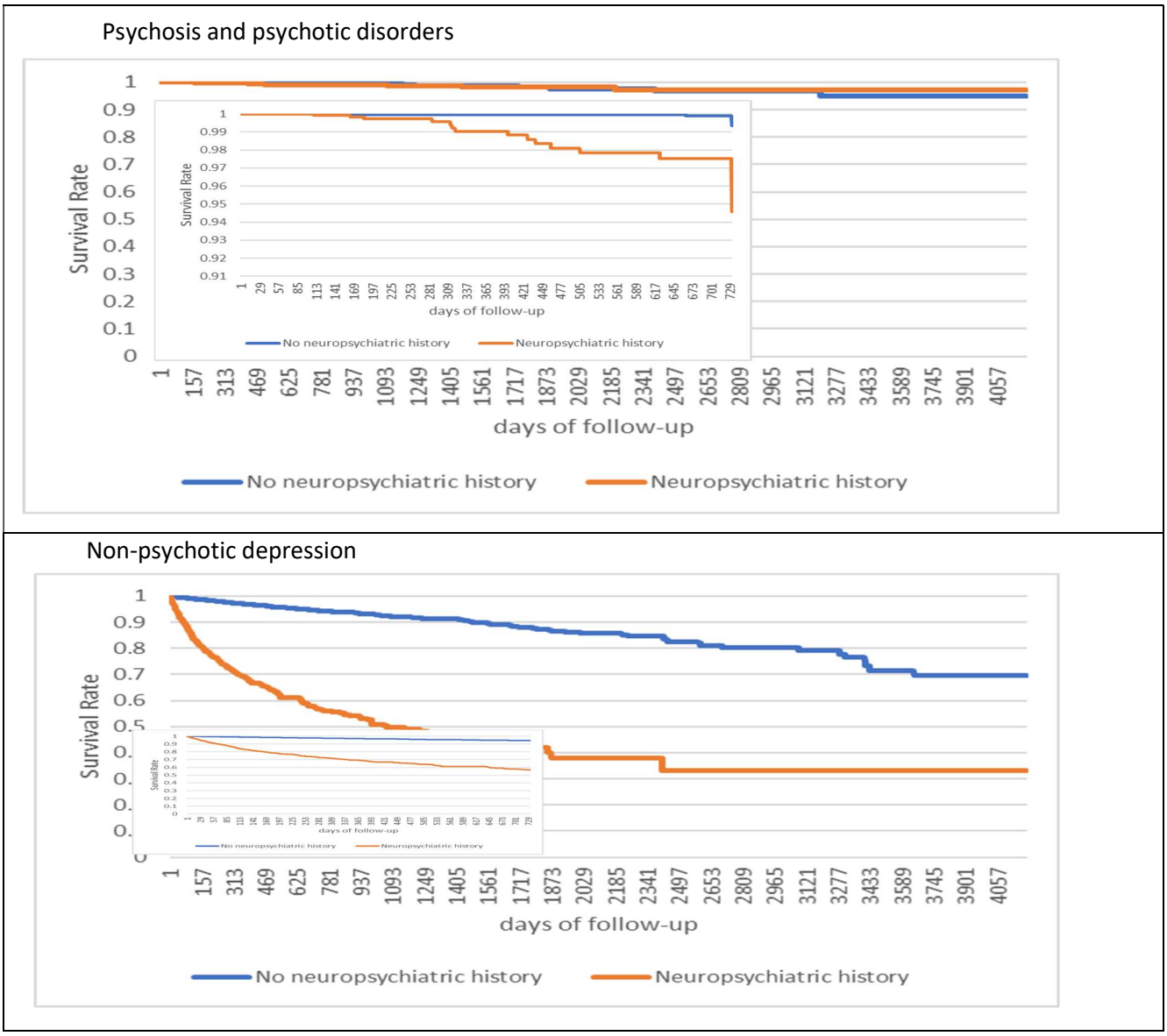
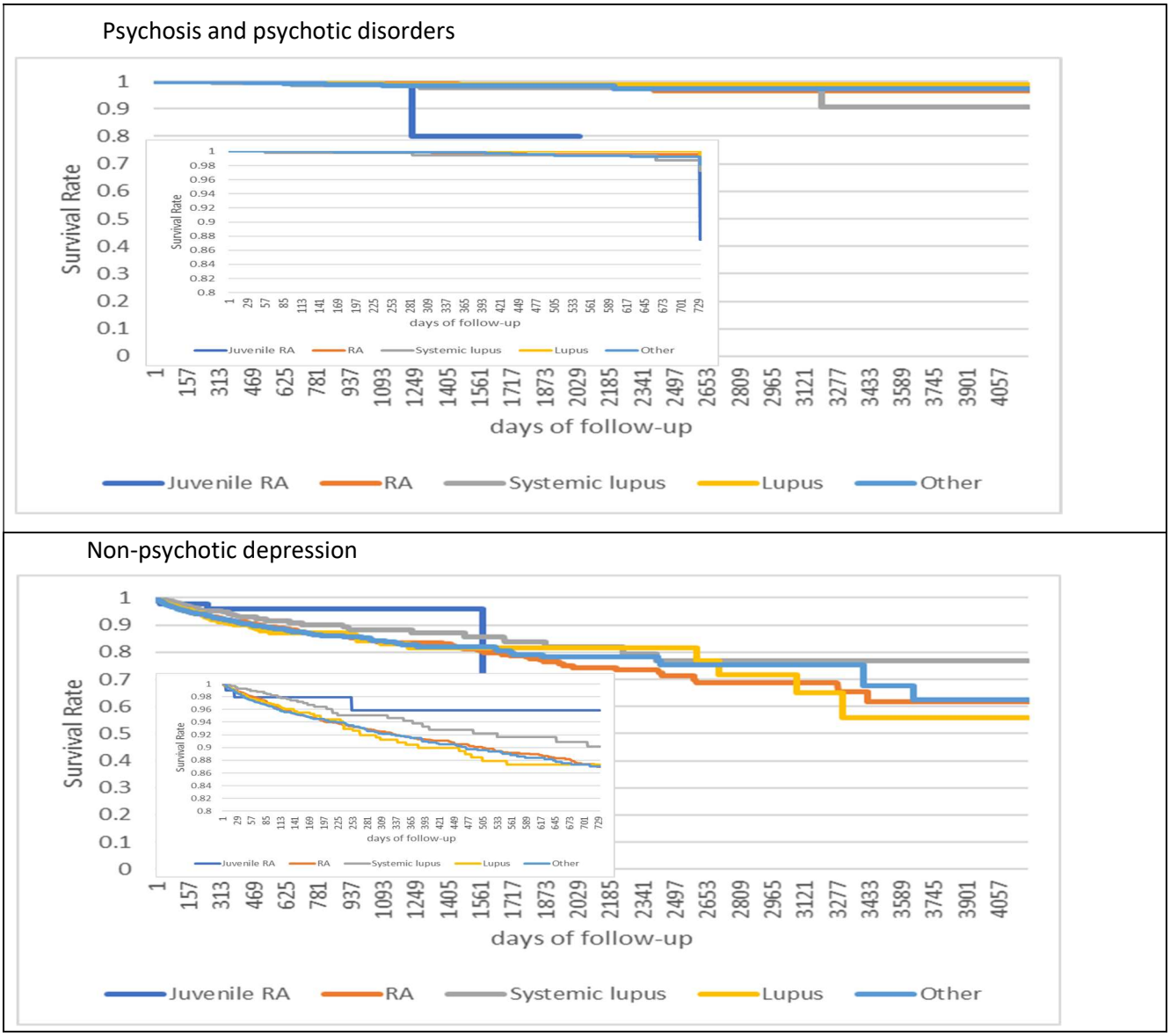


Figure 6. Kaplan Meier survival curves stratified by indication (RA, juvenile RA, lupus, other): HCQ

(for each event, the small graph provides the detailed curve over a shorter time period (0-730 days), then the 0-4200 days period of the large graph).



7.2. Chloroquine

During the analysis of the data, it was noted that there was a high proportion of patients for which a plausible indication for treatment cannot be identified (overall 46%) and this proportion is higher for the first two time periods from before 2000 and 2000-2004 (50.6% and 51.3%) compared with the subsequent three time periods (2005-2009: 41.4%, 2010-2014: 41.9% and 2015-2019: 37.8%).

There are around 100 patients in which the duration of treatment could not be estimated (data not shown), and the algorithm used to estimate the duration of treatment resulted in lower daily doses than expected (mean of 165 mg vs. more than 210 mg expected). When CQ is used for prophylaxis of malaria it is dosed once per week. This dosage is not reflected in the data, and weekly rather than daily dosing makes it particularly challenging to estimate the treatment duration. The usefulness of the algorithm for patients treated with CQ could therefore be questioned.

Due to higher complexity in the data with more variation in expected dosage and treatment duration for CQ compared to HCQ, and due to a relatively high proportion of patients starting treatment before year 2000 (37.3% of patients), when the recording of diagnoses appears to have been less complete, it is not considered meaningful, based on the current data and estimated treatment episodes, to estimate the incidence of neuropsychiatric events in patients treated with CQ.

Therefore, only data relating to patterns of use are presented for IMS ® Disease Analyzer Germany and data for incidence rates of neuropsychiatric events have not been further analysed.

7.2.1. Pattern of use: CQ

Descriptive analyses were performed to describe and summarise the study cohorts (CQ) at baseline: this includes the number of patients exposed, age at first use, sex, year of first use and numbers of prescriptions and exposure windows per patient. This describes indication, the proportion of patients with previous neuropsychiatric diagnoses, and dose of HCQ. The cumulative dose of HCQ at the time of event has been summarised.

Table 1.2 Patient demographic summary

	Chloroquine
Total no of patients	6530
No. of female patients (%)	3784 (57.9%)
Mean age in years (SD)	43.5 (17.1)
Median age (IQR)	44(29 - 57)
Min- max age	0 - 91
No. with missing age information	25
Start year before 2000	2437 (37.3%)
Start year 2000-2004	1135 (17.4%)
Start year 2005-2009	1059 (16.2%)
Start year 2010-2014	1084 (16.6%)
Start year 2015-2019	815 (12.5%)

[1] Three patients had never a diagnosis recorded and have been excluded from the tables below.

Table 2.2. Prescriptions, doses (in mg) and treatment episodes

	Chloroquine
Total no. of patients	6527
Total no. of episodes	7165
Min-max episodes	1-9
Mean episodes (SD)	1.10 (0.43)
Median episodes (IQR)	1.00 (1.00 -1.00)
Total no. of prescription dates	12,843
Min-max prescription dates	1-77
Mean prescription dates (SD)	1.97 (3.78)
Median prescription dates (IQR)	1.00 (1.00-1.00)

Table 3.2. Indications

	Chloroquine
Total no of patients with any prior diagnosis [1]	6500 (99.6%)
No of patients with no prior diagnosis	27 (0.4%)
No of patients with RA	822 (12.6%)
No of patients with juvenile RA	4 (0.1%)
No of patients with lupus	293 (4.5%)
No of patients with systemic lupus	148 (2.3%)
No. of patients with malaria	87 (1.3%)
No. of patients with prophylaxis within 30 days	713 (10.9%)
No. of patients with immunisation within 30 days	1956 (30.0)
No of patients with a prior diagnosis and none of the above diagnoses	3002 (46.0%)
No of patients with other diagnoses with no prior diagnosis of RA, juvenile RA, lupus or systemic lupus	5314 (81.4%)

Table 3.3. Indications over time

	Before 2000	2000-2004	2005-2009	2010-2014	2015-2019
Any prior diagnosis [1]	2432	1127	1051	1080	810
RA	156 (6.4%)	109 (9.7%)	218 (20.7%)	171 (15.8%)	168 (20.7%)
Juvenile RA	1 (0.0%)	0 (0.0%)	2 (0.2%)	1 (0.1%)	0 (0.0%)
Lupus	20 (0.8%)	8 (0.7%)	73 (6.9%)	101 (9.4%)	91 (11.2%)
Systemic lupus	16 (0.7%)	4 (0.4%)	34 (3.2%)	46 (4.3%)	48 (5.9%)
Malaria	5 (0.2%)	18 (1.6%)	32 (3.0%)	20 (1.9%)	12 (1.5%)
Chemoprophylaxis within 30 days	385 (15.8%)	122 (10.8%)	91 (8.7%)	72 (6.7%)	43 (5.3%)
Immunisation within 30 days	817 (33.6%)	368 (32.7%)	265 (25.2%)	294 (27.2%)	212 (26.2%)
No RA, juvenile RA, lupus, systemic lupus	2248 (92.4%)	1007(89.4%)	739 (70.3%)	783 (72.5%)	537 (66.3%)
None of the above	1230 (50.6%)	578 (51.3%)	435 (41.4%)	453 (41.9%)	306 (37.8%)

[1] Diagnoses for which the diagnosis certainty was provided as 'exclusion of', which indicated that the patient did not have the diagnosis, have been excluded.

RA = rheumatoid arthritis. Please note that diagnosis categories are not mutually exclusive. Malaria includes ICD 10 codes B50-B54. Prophylaxis includes ICD 10 code Z29. Immunisation includes ICD 10 codes Z23-Z27.

Table 3.4 Total number of chloroquine prescriptions and recorded mean doses by indication

	Mean daily dose (no. of prescriptions with daily dose)	Mean total no. of prescriptions (mean pack size)
Patients with RA (n=822)	264 (n=283))	4.18 (69.7 tablets)
No of patients with juvenile RA (n=4)	500 (n=1)	4.75 (79.5 tablets)
No of patients with lupus (n=293)	269 (n=81)	5.39 (73.1 tablets)
No of patients with systemic lupus (n=148)	254 (n=45)	5.13 (76.2 tablets)
No. of patients with malaria (n=87)	259 (n=8)	1.14 (33.1 tablets)
No. of patients with prophylaxis within 30 days (n=713)	210 (n=180)	1.18 (31.4 tablets)
No. of patients with immunisation within 30 days (n=1956)	231 (n=275)	1.15 (30.9 tablets)

RA = rheumatoid arthritis. Please note that diagnosis categories are not mutually exclusive. Malaria includes ICD 10 codes B50-B54. Prophylaxis includes ICD 10 code Z29. Immunisation includes ICD 10 codes Z23-Z27.

Table 4.2. Prior neuropsychiatric diseases

	Chloroquine
All patients	6527 (100%)
No of patients with any prior neuropsychiatric diagnosis	868 (13.3%)
No of patients with prior suicidal events	8 (0.1%)
No of patients with prior self-harm events	8 (0.1%)
No of patients with schizophrenia psychosis related events	37 (0.6%)
No of patients with affective psychosis related events	17 (0.3%)
No of patients with non-psychotic affective disorders	841 (12.9%)

8. References

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9. Appendices

Appendix 1

List of hydroxychloroquine products in IMS ® Disease Analyzer Germany

GE6303	QUENSYL UEBERZ.TABL. 200MG 100 (N3)
GE25410	QUENSYL UEBERZ.TABL. 200MG 30 (N2)
GE501950	PLAQUENIL EUP>> DRAG 200MG 100 (N3)
GE3157780	PLAQUENIL EUP>> DRAG 200MG 30 (N2)
GE6970945	QUENSYL FILMTABL 200MG 30
GE7020389	QUENSYL FILMTABL 200MG 100 (N3)
GE10153135	PLAQUENIL EUP>> FILMTABL 200MG 100 (N3)
GE11478385	PLAQUENIL E-M>> FILMTABL 200MG 100 (N3)
GE12077734	PLAQUENIL KHP>> FILMTABL 200MG 100 (N3)
GE12705459	PLAQUENIL GRK>> FILMTABL 200MG 100 (N3)
GE16656627	HYDR.CHLOROQU.ARIS FILMTABL 200MG 100 (N3)
GE16766451	HYDR.CHLOROQU.ARIS FILMTABL 200MG 30
GE17193192	PLAQUENIL BRA>> FILMTABL 200MG 100 (N3)
GE17689371	HYDR.CHLOROQU.EBER FILMTABL 200MG 100 (N3)
GE17724772	HYDR.CHLOROQU.AXC. FILMTABL 200MG 100 (N3)
GE17786381	HYDR.CHLOROQU.AXC. FILMTABL 200MG 30
GE18142059	HYDR.CHLOROQU.EBER FILMTABL 200MG 30

List of chloroquine products in IMS ® Disease Analyzer Germany

GE1041339	RESOCHIN MTK>> TABL 250MG 100 (N3)
GE1044525	RESOCHIN A1H>> TABL 250MG 50 (N2)
GE1044702	RESOCHIN A1H>> TABL 250MG 20 (N1)
GE106850	RESOCHIN INJ LSG AMP 250MG 5 5ML (N2)
GE1124359	RESOCHIN A1H>> TABL 250MG 100 (N3)
GE1143516	RESOCHIN MTK>> TABL 250MG 50 (N2)
GE117532	RESOCHIN EUP>> TABL 250MG 20 (N1)
GE1190430	WEIMERQUIN (WEI) TABL 500MG FT 50 (N3)
GE125118	RESOCHIN SAFT 810MG 75ML (N1)
GE151920	RESOCHINA GRK>> TABL 250MG 20 (N1)
GE158442	WEIMERQUIN (WEI) TABL 250MG 20 (N1)
GE174736	RESOCHIN MTK>> TABL 250MG 20 (N1)
GE1760074	RESOCHINA EUP>> TABL 250MG 100 (N3)
GE192628	RESOCHINA E-M>> TABL 250MG ALT 50 (N2)
GE195642	RESOCHIN KHP>> TABL 250MG 50 (N2)
GE225699	WEIMERQUIN ALT TABL 250MG 20 (N1)
GE2275849	RESOCHINA E-M>> TABL 250MG 20 (N1)
GE256316	RESOCHIN AC9>> TABL 250MG 50 (N2)
GE25725	RESOCHIN TABL JUNIOR 81MG 30
GE25726	RESOCHIN TABL 250MG 100 (N3)
GE25727	RESOCHIN TABL 250MG 20 (N1)
GE25728	RESOCHIN TABL 250MG 50 (N2)
GE259917	WEIMERQUIN ALT TABL 250MG 50 (N2)
GE260882	RESOCHINA E-M>> TABL 250MG ALT 100 (N3)
GE264364	WEIMERQUIN ALT TABL 500MG FT 20 (N2)
GE2870891	RESOCHINA EUP>> TABL 250MG 50 (N2)
GE318771	RESOCHINA GRK>> TABL 250MG 50 (N2)
GE322511	ARTHRABAS FILMTABL 250MG 100 (N3)
GE3429483	RESOCHINA E-M>> TABL 250MG 50 (N2)
GE382461	WEIMERQUIN (WEI) TABL 250MG 100 (N3)
GE391068	RESOCHIN KHP>> TABL 250MG 100 (N3)
GE400194	WEIMERQUIN (WEI) TABL 500MG FT 20 (N2)
GE413858	CHLOROCHIN FILMTABL 250MG 100 (N3)
GE413931	CHLOROCHIN FILMTABL 250MG 20 (N1)
GE414223	CHLOROCHIN FILMTABL 250MG 50 (N2)
GE419469	WEIMERQUIN (WEI) SIRUP 25MG 100ML (N1)
GE419906	RESOCHINA GRK>> TABL 250MG 100 (N3)
GE444879	RESOCHIN KHP>> TABL 250MG 20 (N1)
GE4515953	RESOCHINA BRA>> TABL 250MG 20 (N1)
GE4743184	RESOCHINA BRA>> TABL 250MG 50 (N2)
GE492205	RESOCHIN BRA>> TABL 250MG 50 (N2)
GE507790	RESOCHIN ORI>> TABL 250MG 100 (N3)
GE508416	RESOCHIN EUP>> TABL 250MG 100 (N3)
GE524744	RESOCHINA E-M>> TABL 250MG 100 (N3)
GE533193	WEIMERQUIN (WEI) TABL 500MG FT 10 (N1)
GE560538	WEIMERQUIN (WEI) TABL 250MG 50 (N2)
GE560654	WEIMERQUIN ALT TABL 500MG FT 10 (N1)
GE576340	RESOCHIN BRA>> TABL 250MG 20 (N1)
GE585530	WEIMERQUIN ALT TABL 250MG 100 (N3)

GE627270	RESOCHIN EUP>> TABL 250MG 50 (N2)
GE6578378	RESOCHINA BRA>> TABL 250MG 100 (N3)
GE702467	ARTHRABAS FILMTABL 250MG 50 (N2)
GE706406	RESOCHIN ORI>> TABL 250MG 50 (N2)
GE707714	RESOCHINA REA>> TABL 250MG 20 (N1)
GE802177	RESOCHINA BRA>> TABL 250MG ALT 20 (N1)
GE839097	RESOCHIN AC9>> TABL 250MG 100 (N3)
GE911065	RESOCHINA E-M>> TABL 250MG ALT 20 (N1)
GE976130	RESOCHIN BRA>> TABL 250MG 100 (N3)

List of event codes used for IMS ® Disease Analyzer Germany

- Suicide events and self-harm events: Any of the following ICD 10 codes, combined with a medical event text that indicated either a suicidal event or a self-harm event, which were analysed separately (please note that ICD 10 codes X60-X85, Y10-Y34 and Y87 are not available in IMS ® Disease Analyzer Germany):
    - Z91.5 (personal history of self-harm): For this ICD code we will also include cases without a medical event text
    - Z91.8 (personal history of other specified risk-factors, not elsewhere classified)
    - R45.8 (other signs and symptoms involving emotional state)
    - T14.9 (injury unspecified)
    - Z72.8 (unspecified problem related to lifestyle)
- Schizophrenia-related events: An ICD 10 code of F20 to F29 (schizophrenia, schizotypal and delusional disorders), R44.0 (Auditory hallucinations), R44.1 (Visual hallucinations), R44.2 (Other hallucinations), R44.3 (Hallucinations, unspecified), R44.8 (Other and unspecified symptoms and signs involving general sensations and perceptions)
- Affective psychosis-related events: Any of the following ICD 10 codes:
    - F30 (manic episode)
    - F31 (bipolar affective disorder)
    - F32.3 (severe depressive episode with psychotic symptoms)
    - F33.3 (recurrent depressive disorder, current episode severe with psychotic symptoms)
- Non-psychotic depression and other emotional disorders: Any of the following ICD 10 codes:
    - F32 (depressive episode)
    - F33 (recurrent depressive disorder)
    - F34 (persistent mood disorders)
    - F38 (other mood disorders)
    - F39 (unspecified mood disorder)
    - F60.3 (emotionally unstable personality disorder)

- R45 (symptoms and signs involving emotional state): Any events that have been coded as suicide events or self-harm events will be excluded from this category