Pharmacologie médicale

Bordeaux PharmacoEpi
CIC Bordeaux CIC1401

SALT-II

Study of Acute Liver Transplant

Prolongation & continuation of the SALT-I study
"A study of drug-exposed acute liver failure in European transplant centres"

Final Study Report

Version 1.0

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PASS INFORMATION

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Country of study	France
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MARKETING AUTHORISATION HOLDER(S)

Marketing Authorisation Holder(s)	NA
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1 ABSTRACT

Title	SALT-II Study of Acute Liver Transplant Prolongation & continuation of the SALT-I study "*A study* of *drug-exposed acute liver failure in European transplant centres*"
Keywords	DILI, hepatotoxicity, liver transplantation
Rational and background	The SALT-I study created a network of 55 liver transplant centres in seven European countries. It also accumulated a considerable body of data on drug-exposed acute liver failure in Europe. The national coordinators of these centres have expressed a desire to continue this collaboration and monitor severe acute hepatitis in Europe.
Research question and objectives	To estimate the risk of drug-exposed acute liver failure (ALF) patients registered for liver transplantation (ALFT) in adults, according to the population exposure to the same drugs, over a six-year period (01/01/2008 to 31/12/2013).
Study design	Multicentre, retrospective case-population study of drug-exposed ALFT patients.
Setting	Liver transplant centres in France
Subjects and study size, including dropouts	Cases were from the liver transplant units, after identification from national/local transplant registries. Data collection was completed by trained clinical research assistants by seeking data through hospital medical files.
Variables and data sources	Hospital medical files, CRISTAL database, EGB database
Results	The SALT-II study has exhaustively included all 22 eligible liver transplant centres in France, for all contributed data, proving the feasibility and the operationability of the study at a higher level. Furthermore, pooling of SALT-II data with SALT-I data allowed greater number of ALFT events and therefore a better precision of the risk estimates. Over the 6-year period (2008-2013), 8 341 patients registered for liver transplantation were included in the SALT-II study (1 390 cases per year). The number of cases registered for transplantation has slightly increased since SALT-I study. Demographic characteristics of ALFT cases for the pooled 9-year period (2005-2013) stayed similar to the one for the 6-year period (2008-2013), the demographic proportions remained constant regardless the study period. According to the clinical diagnosis recorded in the CRISTAL database, 559 cases (6.7% of registered cases) were diagnosed with ALFT, which has increased 1.6-fold since SALT-I study when considered as per year (58.6 versus 93 cases, respectively for SALT-I and SALT-II). The main cases were non-overdose drug-exposed ALFT without identified clinical cause, for which SALT-II has identified 82 cases (14.7%) over the 6-year period; this decreased since SALT-I study when considered per year (21.6 versus 13.6 cases, respectively for SALT-I and SALT-II). An important finding of the SALT-II study is that of the 246 drug-exposed ALFT cases without identified clinical cause, 132 (23.6% of ALFT) were acute drug overdose cases. This was more than two-fold increase since SALT-I study when considered per year (10.6 versus 22 cases, respectively for SALT-I and SALT-II). When data were pooled for the pooled 9-year period (2005-2013), non-overdose drug-exposed ALFT cases

	frequency was 16.3 cases. However, acute drug overdose cases remained increased since SALT-I study; 18.2 cases per year. When non-overdose paracetamol-exposed ALFT cases were evaluated, the increase was obvious for the pooled 9-year period when compared to 6-year period SALT-II, and 3-year period SALT-I (55.8% versus 42.7% versus 75.4%). The high incidence rates of ALFT for cases exposed to drugs for treatment for tuberculosis (ATC code J04A), antidepressants (ATC code N06A), direct acting antivirals (ATC code J05A), anxiolytics (ATC code N05B) or antiepileptics (ATC code N03A) need to be further evaluated in complementary data analyses.
Conclusion	SALT-II study results show that acute liver failure leading to transplantation in drug-exposed patients is a rare but important event. Paracetamol exposure at therapeutic doses or at overdose is still the almost exclusive cause for liver transplantation, and has increased in France since SALT-I study period. The reasons for this needs to be further evaluated. The high incidence rates of ALFT for cases exposed to drugs for treatment for tuberculosis, antidepressants, direct acting antivirals, anxiolytics or antiepileptics need to be further evaluated in complementary data analyses. The results of both SALT-II study and pooled SALT/SALT-II helped and provided necessary scientific and organisation preparations for the prospective study, SALT-III, which has already started and ongoing smoothly in France. SALT-III study will eventually provide a better profile and better risk estimations and usage patterns for drug-exposed ALFT, and particularly paracetamol-associated overdoses leading to registration for liver transplantation, as the study will be as well evaluating pharmacogenetic factors for drug-associated ALFT. An outcome not be neglected is also that this study strengthen the key research network of the French liver transplant centres, and showed again the feasibility of networking. The wealth of information and results could thus be worth to help the regulatory authorities for decision-making. The future perspective is to extend both SALT-II and SALT-III in Europe. A new project named EURO-SALT is under preparation, for which ANSM has expressed its interest, and financed a feasibility study, EURO-SALT(f), scheduled for 2016. The new methods to be developed in EURO-SALT are use of hospital information systems to store and extract case data, systematic retrieval of blood samples for pharmacokinetic, toxicological and pharmacogenetic evaluation of drug hepatotoxicity, identifying possible co-factors or drugs that might worsen the prognosis or outcome of the initial liver injury. Linking to claims databases could provide more exposure information. This is a novel issue that has not been yet studied systematically.
Marketing Authorisation Holder(s)	NA
Names and affiliations of principal investigators	The study has been performed by the Bordeaux PharmacoEpi Plateform (BPE) of the Department of Medical Pharmacology CIC Bordeaux CIC1401 (Head of Department Pr Mathieu Molimard and Head of CIC1401 Pr Nicholas Moore). The study is under the scientific responsibility of Pr Ezgi Gulmez. The investigators are hepatologists or liver transplant surgeons of the liver transplant centres.

2 LIST OF ABBREVIATIONS

ADERA	*Association pour le Développement de l'Enseignement et des Recherches auprès des universités, des centres de Recherche et des entreprises d'Aquitaine*
ALF	Acute Liver Failure
ALFT	Acute Liver Failure leading to registration for Transplantation
ATC	Anatomical Therapeutic Chemical
BUF	Bordeaux University Foundation
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CLF	Chronic Liver Failure
CNIL	*Commission Nationale de l'Informatique et des Libertés* (National Commission on Informatics and Freedom)
CNOM	*Conseil National de l'Ordre des Médecins* (National Order of Physicians)
CMV	Cytomegalovirus
CRA (ERA)	Clinical (epidemiology) research assistant
CRF	Case Report Form
CRO	Contract Research Organisation
DDD	Defined Daily Dose
EBV	Epstein Barr Virus
ENCePP	European Network of Centres of Excellence in Pharmacoepidemiology and Pharmacovigilance
HAV	Hepatitis A Virus
HBV	Hepatitis B Virus
HCV	Hepatitis C Virus
HDV	Hepatitis D Virus
HEV	Hepatitis E Virus
HSV	Herpes Simplex Virus
ID	Index Date
ISPE	International Society for Pharmacoepidemiology
NCSCH	National Case Selection Committee Hepatologist
NSAID	Non-Steroidal Anti-inflammatory Drug
OTC	Over-The-Counter
PDD	Prescribed Daily Dose
RIB	*Relevé d'Identité Bancaire*
RPPS	*Répertoire Partagé des Professionnels de Santé*
SC	Steering Committee
SIREN	*Système Informatique du Répertoire des ENtreprises*
SIRET	*Système d'Identification du Répertoire des ETablissements*
URSSAF	*Union de Recouvrement des cotisations de Sécurité Sociale et d'Allocations Familiales*

UK	United Kingdom
ULN	Upper Limit of Normal

3 INVESTIGATORS

The study has been performed by the Bordeaux PharmacoEpi Plateform (BPE) of the Department of Medical Pharmacology CIC Bordeaux CIC1401 (Head of Department Pr Mathieu Molimard and Head of CIC1401 Pr Nicholas Moore). The study is under the scientific responsibility of Pr Ezgi Gulmez.

The investigators are hepatologists or liver transplant surgeons of the liver transplant centres.

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NATIONAL CASE SELECTION COMMITTEE HEPATOLOGIST

France	Pr Georges-Philippe Pageaux

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Regulatory authorisations		CCTIRS approval obtained on 8th July 2013 CNIL approval obtained on 11th July 2013.	
Study set-up	1st semester of 2014	July 2013 to August 2014	
Data collection	September 2014 – 2nd quarter of 2016	September 2014 – June 2015	
Validation of cases		February 2015 – June 2016	
Data analysis	1st quarter of 2016 - 2nd quarter of 2016	2nd quarter of 2016	
Update of final report	2nd quarter of 2016	2nd quarter of 2016	

6 RATIONALE AND BACKGROUND

Acute liver injury has been reported with most drugs, and is one of the more common reasons for drug withdrawal from the market, or for interruption of development. (1-3).

Acute liver reactions range from the simple asymptomatic increase in liver enzymes, to liver transplantation. Asymptomatic increases in liver enzymes, mostly transaminase, are discovered through systematic monitoring of patients, as is done routinely during clinical development, but have no clear clinical safety implication. The usual limit for non-seriousness of increased transaminase is considered to be three times upper limit of normal (ULN). (4, 5) More severe reactions include "Hy's law" cases which combine transaminases above three times ULN, usually above 5 times ULN, with increased bilirubin above twice ULN, without cholestasis and without other causes of liver injury. The most severe cases result in liver failure and often death or liver transplantation. It is the latter cases that have the greatest public health importance.

Among different drug classes, non-steroidal anti-inflammatory drugs (NSAID) have often been involved in liver injury (1, 6) and adverse hepatic reactions have been reported for most NSAIDs. (7) General population studies of hepatic reactions with NSAIDs did not demonstrate a clear difference between NSAIDs for hepatic reactions not leading to transplantation. (8, 9) Because of a suspected greater risk of hepatotoxicity with nimesulide, the CHMP required an epidemiological study of the more severe NSAID-exposed acute liver failure in Europe, those leading to transplantation (ALFT).

This led to the SALT study (Study of Acute Liver Transplant) whose objective was to assess the risk of ALFT, in patients without identified clinical aetiology, exposed to NSAIDs, on a 3-year period (2005-2007), in seven European countries. (10) This first SALT study has been followed by SALT-II, with the same methodology except causality assessments and on a 6-year period (2008-2013), with the objective to assess the ALFT risk associated with all drugs including herbal medicines.

In the beginning, the SALT-II study has been anticipated for the five main countries contributing to SALT-I: France, Ireland, Italy, Netherlands and United Kingdom (very few or no drug-exposed cases of ALFT in Greece and Portugal). However, the extension of SALT-II

together with SALT-III is currently the objective of a new study, EURO-SALT, for which a feasibility study financed by ANSM is ongoing. Therefore, SALT-II has been conducted only in France, and this study report presents the results only from France. Since results concern only French data, comparison of event rates between countries (the first secondary objective) has not been available.

7 RESEARCH QUESTION AND OBJECTIVES

The primary objective of SALT-II study was to estimate the risk of drug-exposed ALFT in adults, according to the population exposure to the same drugs, over a six-year period (01/01/2008 to 31/12/2013).

8 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
V2.0	23/12/2013			Submitted version to regulatory authorities in France (CCTIRS, CNIL)
V3.0	07/03/2014			Amended version following the ENCePP requirements

The final version of the study protocol is the version v3.0 of 07/03/2014 (Appendix 1.1).

9 RESEARCH METHODS (FRENCH PART)

9.1 STUDY DESIGN

Case-population approach was used.

As in the SALT-I study, the patients registered on the transplant waiting list were identified from the national transplant registry (CRISTAL). All patients registered for liver transplantation over a six-year period (01/01/2008 – 31/12/2013) were identified. According to the diagnosis indicated in the CRISTAL database, the CLF cases were separated from the ALFT patients or from cases not clearly defined as CLF. The CRF-1 was completed with data extracted from CRISTAL. For the two further categories of ALFT or cases not clearly defined, the CRA(s) of the Coordinating Centre abstracted data from the medical files at the participating centres under the supervision of the centre's physician. Cases were then further classified as ALFT or CLF, enclosing the scanned documentation of liver biopsy / histology to the CRF-1. For all ALFT cases (validated by the centre's physician), CRF-2 was completed by CRA from medical files at the participating centre. CRF-2 was accompanied by the documentation of the relevant clinical raw data. For all ALFT cases without identified clinical cause (validated by the centre's physician), CRF-3 was completed by CRA from medical files at the participating centre. CRF-3 was accompanied by a copy of the relevant clinical raw data. All necessary source data were anonymized and scanned on site, or photocopied and scanned at the Coordinating Centre. Data input into the study database was done onsite if possible or at the Coordinating Centre using scanned data.

Case selection was done in the same three-step way as of SALT-I: A brief documentation of each case, containing the essential data to conclude on all the three selection steps, was prepared by the Coordinating Centre staff and sent to the Case Selection Committee Hepatologist (NCSCH) in order to minimise the workload of the NCSCH. The NCSCH reviewed only ALFT cases and cases not clearly defined as CLF, and then transmitted his conclusions to the Coordinating Centre. At the first step of case selection, he validated or not the diagnosis of ALF or diagnosis of CLF. At the second step of case selection, the ALFT

cases were classified into ALFT with or without clearly identified clinical cause. At the third step, the NCSCH reviewed all ALFT cases without identified clinical cause to classify into cases with acute drug overdose (with or without suicidal intent), or cases exposed to drugs 30 days prior to ID, or cases not exposed to drugs. The NCSCH determined the ID (date of the onset of the liver disease).

9.2 SETTING

9.2.1 Participation of Liver Transplant Centres

The SALT-II study was performed in French liver transplant centres.
All liver transplant centres having participated to SALT-I study, as well as one new centre opened since the end of SALT-I, were contacted and were invited to participate. Finally, 22 liver transplant centres were active at the time of the study setup, all accepted to participate, and provided data.

9.2.2 Regulatory Aspects

Concerning the regulatory aspects, the final protocol was submitted to the Competent Authorities according to the French regulatory requirements:

Contracts

The National Order of Physicians (*Conseil National de l'Ordre des Médecins*, CNOM) reviewed the study protocol and the model of agreement concluded between the participating physicians and the coordinating centre (article L.4113-6 of Public Health Code). The study received a constructive notice because of the delayed response from the Order.

Protection of human subjects

The SALT-II study has not been submitted to the Committee for the Protection of Persons for the Southwest and Overseas III (*Comité de Protection des Personnes, Sud-Ouest et Outre Mer III, CPP– SOOM III*), since the methodology of the study did not require it.

Data protection

The study protocol received the favourable opinion from the *Comité Consultatif sur le Traitement de l'Information en matière de Recherche dans le domaine de la Santé* (CCTIRS) on 8th July 2013. The *Commission Nationale de l'Informatique et des Libertés* (CNIL) authorised the conduct of the study on 11th July 2013.

9.3 SUBJECTS

9.3.1 Case definition

The cases fulfilling the following eligibility criteria were considered for data collection: (10)

- Adult patients of ≥18 years of age at the time of registration on the transplantation list,
- Patient registered on the transplantation list between 1st January 2008 and 31st December 2013, whether the transplantation was actually performed or not,
- Patients who are residents of the country where they were registered.

The non-eligibility criteria were:

- Patients <18 years of age at the time of registration on the transplantation list,
- Patients not resident in the selected countries.

9.3.2 Case identification

All patients registered for liver transplantation for any reason at eligible centres within the study period were identified through the national transplant list (CRISTAL).

Criteria for several registrations on the transplant list were as follows:

1) If the case was registered on the transplantation list several times with the first registration due to ALF, the first registration has been taken and the following registrations were noted;

2) If the case was registered on the transplantation list several times with the first registration due to CLF and any of the following due to ALF, the first registration for ALF has been taken and the first registration was noted;

3) If the case was registered on the transplantation list several times due to CLF at each time, the first registration has been taken and the following registrations were noted;

4) If the case was registered on the transplant list before 01/01/2008 and re-registered another time within the study period, the registration within the study period (considering the rules above) has been taken, and the registration before 2008 was noted.

9.3.3 Case selection

The case selection was a three-step process, done by the National Case Selection Committees after data collection done by the CRA(s) of the Coordinating Centre:

The first step of case selection identified patients with ALF and those with diagnoses other than ALF (chronic liver failure, CLF), for which succinct demographic were collected (CRF-1).

In the second step, patients with ALFT separated into those with (*i.e.* viral hepatitis, auto-immune hepatitis, etc.) or without an identified clinical cause. Patients with an identified clinical cause were not be further assessed for drug exposure (CRF-2).

In the third step, for ALFT patients without an identified clinical cause, all information on drug use were documented under the control of the NCSCH (CRF-3). The NCSCH classified these cases into:

- cases with acute drug overdose (with or without suicidal intent),
- cases exposed to drugs 30 days prior to ID,
- cases not exposed to drugs.

and determined for each one the ID (date of the onset of the liver disease) and transmitted his conclusions to the study coordinating centre. (10)

9.4 VARIABLES

9.4.1 Index date and exposure

The index date (ID) was the date of onset of liver disease: date of initial symptoms or date of laboratory evidence such as elevation of liver enzymes or date of encephalopathy. These dates were determined and validated by the NCSCH.

For all drugs, including herbal medicines, the exposure window selected was within 30 days prior to ID. The 30-day time window was chosen with reference to the reference causality method for drug-related hepatotoxicity based on international consensus conferences. (5, 11-13) Other exposure windows (90, 15 and 7 days) have been used for sensitivity analyses. (10)

9.4.2 Data collected

CRF-1: All patients registered for liver transplantation

Data collected on CRF-1 constituted the basis for the first step of case selection, *i.e.* for separating ALF from non-acute liver failure. CRF-1 was the only set of data collected for patients rejected at the first step such as patients with non-acute liver failure (CLF) and was validated by the NCSCH.

CRF-1 recorded some demographic and clinical data such as:

- Age, sex,
- Date of registration on the liver transplant list,
- Indication for transplantation (diagnosis),
- Other parameters…

CRF-2: Patients registered for ALF

CRF-2 recorded:

- Viral hepatitis (HAV, HBV, HCV, HEV, CMV, EBV, HSV, others),
- Autoimmune hepatitis,
- Other causes (liver ischemia, Wilson's disease, toxic non-drug [i.e. mushrooms, CCL4]),
- Alcohol consumption.

CRF-3: Patients with ALFT without defined clinical cause

For each drug, the following information were recorded in CRF-3:

- Information on drug use (for each drug recorded; name, dose / day, route of administration, indication, start and stop dates),
- Information on drug overdose (name, amount, drug analysis in blood if available),
- Information on possible prechallenge history (name, if the drug is associated with a liver failure).

9.5 DATA SOURCES AND MEASURMENT

Three different datasets were generated for subjects registered in the transplant waiting list, one at each step of the case validation process. CRF-1 was completed using data extracted from CRISTAL database. CRF-2 and CRF-3 were completed by CRA with data abstracted from patient medical files (paper medical files or electronic medical files, depending of the centre equipment), this under the validation of the local physician of the transplant centre.

9.6 BIAS

Bias have been described in Discussion section.

9.7 STUDY SIZE

The number of subjects included in the study was estimated from the results of the SALT-I study. (14)

The SALT-I study identified 104 drug-exposed/without identified clinical cause cases of ALFT in France over the three-year study period, out of 181 cases of ALFT. Over the six years of SALT-II, it was expected that 360 all-cause ALFT and 200 drug-associated ALFT

are identified, so that total numbers would reach 540 ALFT and over 310 drug-associated ALFT.

9.8 DATA TRANSFORMATION

The derived variables and the decision-making rules are detailed in the Statistical Analysis Report (SAR) in Appendix 1.2.

9.9 STATISTICAL METHODS

A detailed Statistical Analysis Plan (SAP) was developed and filed before database lock. Statistical analyses have been carried out using SAS® software (SAS Institute, North Carolina, USA, current version), following the analysis plan.
The Statistical Analysis Report (SAR) presenting the details of the Statistical Analysis Plan, and Tables of results are enclosed to this report (Appendix 1.2).

9.9.1 Main summary measures

Descriptive analysis:

A descriptive analysis of all drug-exposed cases of ALFT has been performed.

Endpoints were estimated as follows:

- **Incidence rate per billion DDD for six years:**

This was equal to the ratio of the number of cases of ALFT without identified clinical cause exposed to a specific drug to the total number of DDD of this specific drug calculated in the EGB for the period 2008-2013 (extrapolated to the French population), multiplied by 1 billion. This indicator was calculated for all and for each drug;

- **Incidence rate per billion patients for six years:**

This was equal to the ratio of the number of cases of ALFT without identified clinical cause exposed to a specific drug to the total number of patients exposed to this specific drug in the EGB for the period 2008-2013 (extrapolated to the French population), multiplied by 1 billion. This indicator was calculated for all and for each drug;

- **Incidence rate per billion patient-years:**

This was equal to the ratio of the number of cases of ALFT without identified clinical cause exposed to a specific drug to the total number of patient-years exposed to this specific drug in the EGB for the period 2008-2013 (extrapolated to the French population), multiplied by 1 billion. This indicator was calculated for all and for each drug.

The estimation of the rates (with a 95% CI from a Poisson distribution) was expressed in cases per billion.

All different per drug rates of ALFT were described with forest plots.

The size of the reference population has been extrapolated for the period 2008-2013 according to age and gender structure of the French population (from the *Institut National de la Statistique et des Etudes Economiques*) with a multiplier. This coefficient was calculated as the total number of people living in France over one year to the total number of patients present in the EGB for that year.

Pooling:

Data of SALT-II have been pooled with data of the previous SALT-I study to estimate the frequency of ALFT identified in nine years (2005-2013). This allowed a greater number of events and a better precision of the risk estimates.

9.9.2 Main statistical methods

9.9.2.1 Reference population

The reference population has been selected in the *Echantillon Généraliste des Bénéficiaires* (EGB) and corresponds to patients

- included and affiliated to CNAMTS (general regimen) in the EGB,
- 18 years old or older,
- without active cancer

The size of the reference population has been extrapolated for the period 2008-2013 according to age and gender structure of the French population (from the *Institut National de la Statistique et des Etudes Economiques*) with a multiplier. This coefficient was calculated as the total number of people living in France over one year to the total number of patients present in the EGB for that year.

9.9.2.2 Comparator data

Drug utilisation patterns

Drug utilisation patterns used to compute number of exposed patients and patient characteristics for stratification or normalization were obtained from the *Echantillon Généraliste des Bénéficiaires* (EGB) in France (10, 15, 16).

Computing numbers of exposed users

Data of SALT-II have been pooled with data of the previous SALT-I study to estimate the frequency of ALFT identified in nine years (2005-2013). This allowed a greater number of events and a better precision of the risk estimates.

Data elements for reference populations

- drug dispensations from 1st January 2008 to 31st December 2013: name, CIP and ATC code, date of dispensation, number of packs dispensed, dose, date of prescription,
- demographic characteristics of concerned subjects: gender, year of birth,
- LTD status of concerned subjects: ICD-10 codes, starting and ending date,
- hospital discharge summaries from PMSI of concerned subjects: ICD-10 diagnosis codes (primary, related, and associated diagnoses), date and duration of hospitalisation and diagnosis-related groups (Homogeneous group of patients GHM (*Groupe Homogène de Malades)* and Homogeneous group of Stays GHS (G*roupe Homogène de Séjours*)).

9.9.3 Missing values

For each variable described, the presence and number of cases with missing data has been reported:

- For the quantitative variables: the number of subjects with a missing data is indicated in brackets next to the number of subjects with an entered value. The distributions were estimated only from entered values.
- For the qualitative variables: the modality "not done" is considered as a full modality, so that its ratio has been calculated relative to the referent total number. For the other modalities, the estimation of proportions takes into account of the "not done" percentage.

No imputation of missing data has been performed in these analyses.

9.9.4 Sensitivity analyses

Sensitivity analyses have been performed using different sources of information to determine the size of populations at risk, based on dispensation and reimbursement data (CNAM-TS Medicam data) and usage data determined from the information about the actual or theoretical

use of products: for DDD (primary analysis) as defined by the WHO Nordic collaborating centre on drug statistics methodology, or depending on usage patterns identified by dispensation, taking as denominator the total consumption in DDD, in patient-years (PDD/365), or patient numbers (based on patterns of use). The study included all drugs families found present in at least five cases.

Sensitivity analyses have been performed for different exposure windows of interest (from 7 to 90 days).

9.9.5 Amendments to the statistical analysis plan

The version of the Statistical Analyses Plan used for the analyses of SALT-II study is the version v0.5 of 21/01/2016.

9.10 QUALITY CONTROL

A random set of the abstracted data has been verified for quality and completeness of abstraction by an independent quality control (QC) team, comparing abstracts with original data from scanned data.

10 RESULTS

10.1 REMINDER OF THE SALT-I STUDY RESULTS

The results of the SALT-I study in France should be summarised for the interpretation of pooled results with SALT-II.

In France, 20 of 21 (95%) liver transplant centres have participated and contributed data to SALT-I.

In these 20 contributing centres, 3 284 patients were identified on liver transplantation waiting lists within 90-days prior to index date. 3 103 patients (94.5%) were listed for CLF and 181 (5.5%) for ALFT. For 5 ALFT patients (2.8%), the medical files were missing or incomplete, and case characteristics could not be ascertained. In 72 (39.8%), ALFT was explained by a defined clinical aetiology, and these cases were not further explored for drug exposure. These were hepatitis B viral hepatitis (34.7%), autoimmune hepatitis (18.3%), other viruses (7.3%), mushroom toxicity (6.0%), Wilson's disease (5.5%), arterial thrombosis or Budd-Chiari syndrome (6.8%), and various other causes (*i.e.*, acute alcoholic or post-traumatic). In 176 analysable ALFT cases (97%), all clinical aetiologies were eliminated and these cases were considered as clinically unexplained. Of these 104 ALFT cases without clinical cause, seven (3.9% of analysable ALFT) were without drug exposure within 30 days before index date (ID, date of the onset of the liver disease). Of the 97 ALFT cases with drug exposure within 30 days prior to index date (ID), 32 (18.6% of analysable ALFT) were acute drug overdose cases; 65 (36.9% of analysable ALFT) were non-overdose cases: Nine (5.1% of analysable ALFT) to at least one NSAID, and 56 (31.8% of analysable ALFT) to drugs other than NSAIDs. Over 60% were female, mean age was 39.7 (±12.5) years, and 67% were ultimately transplanted.

Nine cases were exposed to a total of 10 NSAIDs within 30 days prior to ID. All nine NSAID-exposed ALFT cases were also exposed to other drugs, including paracetamol in eight (88.9%). Of the 56 non-NSAID and non-overdose cases, 41 (73.2%) were exposed to non-overdose paracetamol within 30 days before ID, and 49 (75.4%) of all 65 non-overdose cases. Thirty-one (96.9%) of the 32 overdoses were attributed to paracetamol. The overall NSAID event rate was 1.35 (95%CI 0.62; 2.57) ALFT cases per million treatment-years, corresponding to 3.56 cases per billion DDD. The most common five NSAIDs were ibuprofen, ketoprofen, diclofenac, nimesulide and niflumic acid. In the SALT-I study, ibuprofen had the lowest rate of ALFT per treatment-year (1.80, 95%CI 0.49; 4.60) while niflumic acid had the highest (9.21, 95%CI 0.28; 51.28). As the 95%CI were large, there was

no statistical difference between the rates of ALFT associated with the different NSAIDs. Over the same period, 80 cases were exposed to paracetamol within 30 days before ID, 49 of which without overdose, resulting in ALFT rates of 3.72 (95%CI 2.75; 4.91) per million treatment-years for non-overdose paracetamol and 6.07 (95%CI 4.81; 7.55) per million treatment-years when overdoses were included. Confidence intervals did not overlap with those of event rates for all NSAIDs pooled. These results remained consistent over the sensitivity analyses, such as increasing the exposure window to 90 days, or reducing it to 15 or 7 days, or removing NSAID-exposed cases also exposed to paracetamol, or including cases with paracetamol overdose that were also exposed to NSAIDs. (14)

10.2 RESULTS OF SALT-II AND POOLED RESULTS OF SALT-I / SALT-II

The results of SALT-II and the results of SALT-I/SALT-II are presented in summarised Tables (with Arabic numerals) in the main part of the report. All Tables of results are presented in the Statistical Analyses Report, referenced in this study report with Arabic numerals, and enclosed in Appendix 1.2.

10.2.1 Population

10.2.1.1 Participants

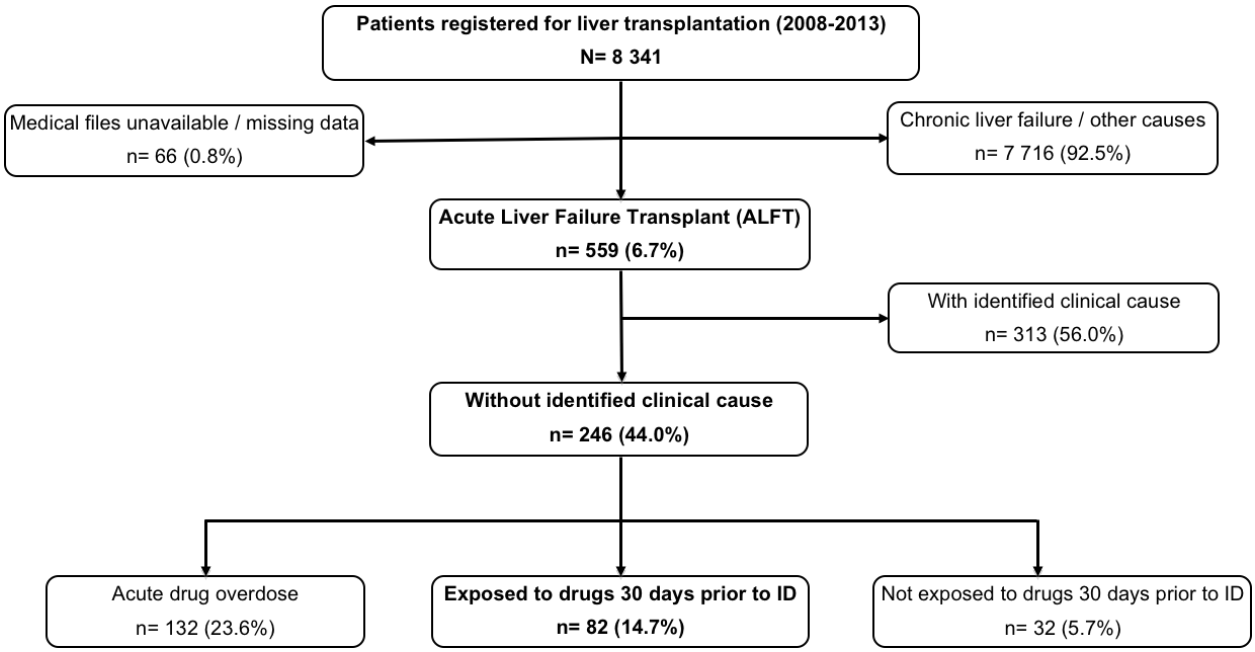
The 21 eligible liver transplant centres of the SALT-I study, as well as one new centre opened since the end of the study, were contacted and invited to participate. A total of 22 liver transplant centres were active at the time of the study setup, all accepted to participate, and contributed data.

10.2.1.2 Case inclusion in SALT-II (6-year period, 2008-2013)

8 383 patients registered for liver transplantation between 1st January 2008 and 31st December 2013 have been identified in the CRISTAL (National Transplant Database). Forty-two cases were excluded (not resident in France or aged less than 18 years old). Overall, 8 341 cases were included in the SALT-II study.
According to the clinical diagnosis recorded in the CRISTAL database, 7 716 cases (92.5% of the registered cases) were identified as CLF, 559 cases (6.7% of registered cases) as ALFT and 66 cases (0.8% of registered cases) for which the diagnosis could not be determined because of missing data or unavailability of the corresponding medical files on site.

Of the 559 ALFT identified cases, 313 (56.0% of ALFT cases) have been considered “with identified clinical cause” and 246 (44.0% of ALFT cases) “without identified clinical cause”. These 246 cases have been reviewed and classified by the NCSCH taking into account the exposure window of 30 days prior to index date. Among them, 132 cases (23.6% of ALFT) have been classified as “acute drug overdose”, 82 cases (14.7% of ALFT) as “exposed to drugs 30 days prior to ID”, and 32 cases (5.7% of ALFT) as “not exposed to drugs 30 days prior to ID” (Figure 1).

Figure 1. Case inclusion in SALT-II (6-year period, 2008-2013).



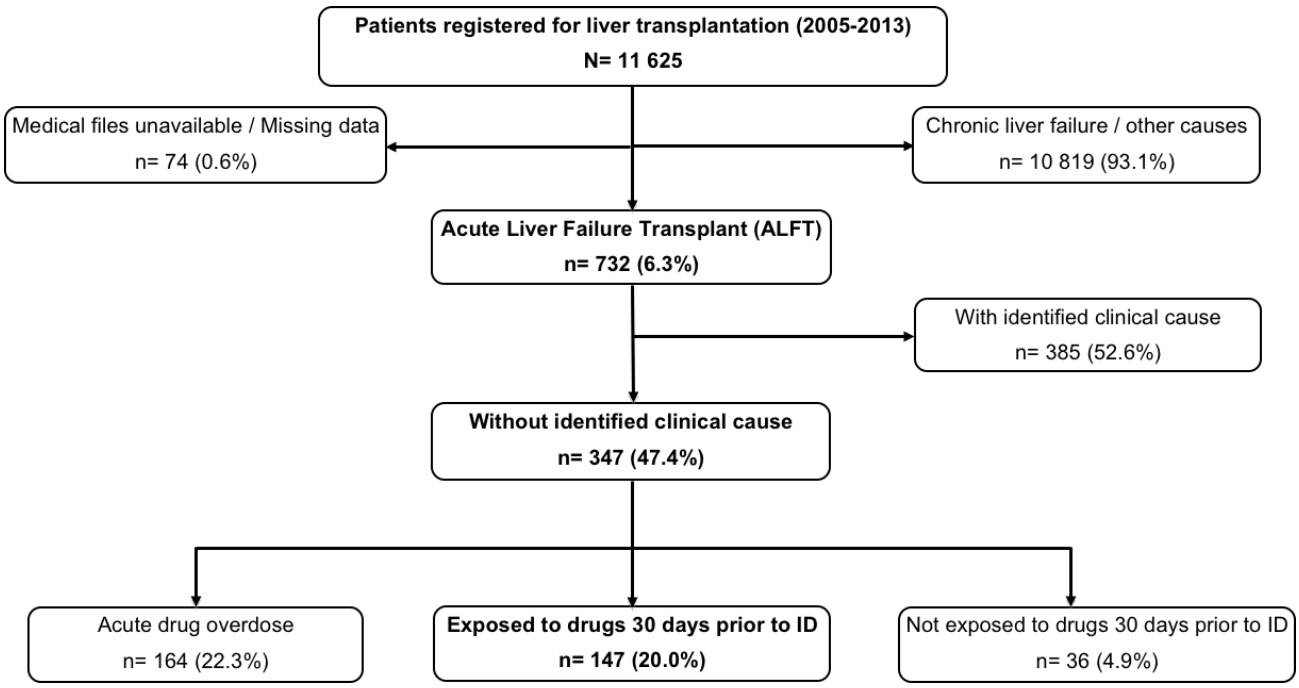
10.2.1.3 Case inclusion in pooled SALT-I/SALT-II (9-year period, 2005-2013)

11 745 patients registered for liver transplantation between 1st January 2005 and 31st December 2013 have been identified in the CRISTAL database (French National Transplant Database). 120 cases were excluded (not resident in France or aged less than 18 years old or patient refusing to participate). Overall, 11 625 cases were included.

According to the clinical diagnosis recorded in the CRISTAL database, 10 819 cases (93.1% of the registered cases) were identified as CLF, 732 cases (6.3% of registered cases) as ALFT, and 74 cases (0.6% of the registered cases) for which the diagnosis could not be determined because of missing data or unavailability of the corresponding medical files on site.

Of the 732 ALFT identified cases, 385 (52.6% of ALFT cases) have been considered "with identified clinical cause" and 347 (47.2% of ALFT cases) "without identified clinical cause". These 347 ALFT cases have been reviewed and classified by the NCSCH taking into account the exposure window of 30 days prior to ID. Of these, 164 cases (22.3% of ALFT) have been classified as "acute drug overdose, 147 cases (20.0% of ALFT) as "exposed to drugs 30 days prior to ID", and 36 cases (4.9% of ALFT) as "not exposed to drugs 30 days prior to ID" (Figure 2).

Figure 2. Case inclusion in pooled SALT-I/SALT-II (9-year period, 2005-2013).



10.2.2 Descriptive data of ALFT cases without identified clinical cause

10.2.2.1 Demographic characteristics

A- SALT-II Study (6-year period, 2008-2013)

The demographic description of the 246 ALFT cases "without identified clinical cause" according to the drug exposure in the 30 days prior to index date for the 6-year study period (2008-2013) is presented in Overall, 65.0% were female. There were more females (72.7%) in "acute drug overdose" cases compared to "not exposed to drugs" (60.9%), and "exposed to drugs" (54.9%). Mean age was 39.9 (±13.4) years and more than seven patients out of ten (74.3%) were aged less than 50 years. Drug-exposed ALFT cases were older (43.8 (±12.9) years) while mean ages were 42.2 (±15.0) years for cases "not exposed to drugs", and 36.9 (±12.6) years for "acute drug overdose" cases, respectively. Liver transplantation was performed for 68.7%, and varied from 59.1% for "acute drug overdose" cases to 78.0% for cases "exposed to drugs", and to 87.0% for cases "not exposed to drugs". (Table 1).

Table 1. Demographic characteristics of ALFT cases "without identified clinical cause" according to drug exposure within the 30 days prior to index date for the 6-year period (2008 to 2013).

	Acute drug overdose n = 132	Exposed to drugs n = 82	Not exposed to drugs n = 32	Total n = 246
Gender, n (%)				
Male	36 (27.3)	37 (45.1)	13 (40.6)	86 (35.0)
Female	96 (72.7)	45 (54.9)	19 (59.4)	160 (65.0)
Age at registration in transplant list (in years)				
Size (missing)	132 (0)	82 (0)	32 (0)	246 (0)
Mean (± SD)	36.9 (12.6)	43.8 (12.9)	42.2 (15.0)	39.9 (13.4)
Median	35.5	43.5	38.0	38.5
[p25% - p75%]	[27.0; 47.0]	[34.0; 54.0]	[33.0; 55.0]	[29.0; 50.0]
[Min - Max]	[18.0; 66.0]	[18.0; 69.0]	[21.0; 76.0]	[18.0; 76.0]
Age at registration in transplant list (in categories), n (%)				
[18 - 30[years	47 (35.6)	12 (14.6)	6 (18.8)	65 (26.4)
[30 - 40[years	33 (25.0)	21 (25.6)	12 (37.5)	66 (26.8)
[40 - 50[years	29 (22.0)	19 (23.2)	4 (12.5)	52 (21.1)
[50 - 60[years	17 (12.9)	21 (25.6)	5 (15.6)	43 (17.5)
≥ 60 years	6 (4.5)	9 (11.0)	5 (15.6)	20 (8.1)
Transplanted, n (%)	78 (59.1)	63 (76.8)	28 (87.5)	169 (68.7)
Year of registration in transplant list, n (%)				
2008	15 (11.4)	11 (13.4)	6 (18.8)	32 (13.0)
2009	16 (12.1)	14 (17.1)	3 (9.4)	33 (13.4)
2010	25 (18.9)	21 (25.6)	7 (21.9)	53 (21.5)
2011	17 (12.9)	13 (15.9)	7 (21.9)	37 (15.0)
2012	27 (20.5)	7 (8.5)	2 (6.3)	36 (14.6)
2013	32 (24.2)	16 (19.5)	7 (21.9)	55 (22.4)

The characteristics of ALFT cases "without identified clinical cause" according to different exposure windows (90, 15, and 7 days prior to index date) in the study period are presented in Tables 2, 3 and 4 of Appendix 1.2.

B- Pooled SALT-I/SALT-II (9-year period, 2005-2013)

The demographic characteristics of the 347 ALFT cases "without identified clinical cause" according to the drug exposure within 30 days prior to index date for the pooled 9-year study period is presented in Table 2.

Overall, 65.1% were female. There were more females (71.3%) in the "acute drug overdose" group compared to cases "not exposed to drugs" (63.9%) and the "exposed to drugs" (58.5%). Mean age was 39.8 (±13.1) years, and more than seven patients out of ten (74.9%) were aged less than 50 years. Drug-exposed ALFT cases were older (42.4 (±13.0) years) while mean ages were 41.7 (±14.5) years for cases "not exposed to drugs", and 37.0 (±12.3) years for "acute drug overdose" cases. Liver transplantation was performed for 68.6%, and varied from 59.1% for "acute drug overdose" cases to 74.1% for "exposed to drugs" group, and to 88.9% for cases "not exposed to drugs".

Demographic characteristics of ALFT cases for the pooled 9-year period (2005-2013) stayed similar to the one for the 6-year period (2008-2013), the demographic proportions remained constant regardless the study period.

Table 2. Demographic characteristics of ALFT cases "without identified clinical cause" according to drug exposure within the 30 days prior to index date for the pooled 9-year period (2005 to 2013).

	Acute drug overdose n = 164	Exposed to drugs n = 147	Not exposed to drugs n = 36	Total n = 347
Gender, n (%)				
Male	47 (28.7)	61 (41.5)	13 (36.1)	121 (34.9)
Female	117 (71.3)	86 (58.5)	23 (63.9)	226 (65.1)
Age at registration in transplant list (in years)				
Size (missing)	164 (0)	147 (0)	36 (0)	347 (0)
Mean (± SD)	37.0 (12.3)	42.4 (13.0)	41.7 (14.5)	39.8 (13.1)
Median	36.0	42.0	38.0	39.0
[p25% - p75%]	[27.5;47.0]	[33.0;52.0]	[33.0;54.0]	[29.0;50.0]
[Min - Max]	[18.0;66.0]	[18.0;69.0]	[21.0;76.0]	[18.0;76.0]
Age at registration in transplant list (in categories), n (%)				
[18 - 30[years	56 (34.1)	27 (18.4)	7 (19.4)	90 (25.9)
[30 - 40[years	42 (25.6)	37 (25.2)	14 (38.9)	93 (26.8)
[40 - 50[years	35 (21.3)	37 (25.2)	5 (13.9)	77 (22.2)
[50 - 60[years	25 (15.2)	32 (21.8)	5 (13.9)	62 (17.9)
≥ 60 years	6 (3.7)	14 (9.5)	5 (13.9)	25 (7.2)
Transplanted, n (%)	97 (59.1)	109 (74.1)	32 (88.9)	238 (68.6)
Year of registration in transplant list, n (%)				
2005	7 (4.3)	18 (12.2)	2 (5.6)	27 (7.8)
2006	12 (7.3)	20 (13.6)	0 (0.0)	32 (9.2)
2007	13 (7.9)	27 (18.4)	2 (5.6)	42 (12.1)
2008	15 (9.1)	11 (7.5)	6 (16.7)	32 (9.2)
2009	16 (9.8)	14 (9.5)	3 (8.3)	33 (9.5)
2010	25 (15.2)	21 (14.3)	7 (19.4)	53 (15.3)
2011	17 (10.4)	13 (8.8)	7 (19.4)	37 (10.7)
2012	27 (16.5)	7 (4.8)	2 (5.6)	36 (10.4)
2013	32 (19.5)	16 (10.9)	7 (19.4)	55 (15.9)

The characteristics of ALFT cases "without identified clinical cause" according to different exposure windows (90, 15, and 7 days prior to index date) in the study period are presented in Tables 17, 18 and 19 of Appendix 1.2.

10.2.2.2 Drug exposure (30-days prior to index date)

A- SALT-II Study (6-year period, 2008-2013)

Of the 246 ALFT cases "without identified clinical cause", about seven out of ten cases (66.7%) were exposed to other analgesics and antipyretics (ATC code N02B), particularly paracetamol: 57.3% of cases exposed to paracetamol without combinations (ATC code N02BE01) (Table 3), and 67.1% to paracetamol, plain and combination (ATC codes N02BE01, N02BE51, N02BE71, N02AA59 and N02AX52) (Table 4).

Of these 246 cases, two cases out of ten were exposed to anxiolytics (ATC code N05B) and/or antidepressants (ATC code N06A) (22.0%, and 17.1%, respectively), and one case out of ten was exposed to antiepileptics (ATC code N03A), NSAID (ATC code M01A), and/or hypnotics and sedatives (ATC code N05C) (10.2%, 9.8%, and 9.3%, respectively) (Table 3).

Of the 82 drug-exposed ALFT cases, about two out of five cases (45.1%) were exposed to other analgesics and antipyretics (ATC code N02B), particularly paracetamol: 39.0% of cases exposed to paracetamol without combinations (ATC code N02BE01) (Table 3) and 42.7% to paracetamol, plain and combination (ATC codes N02BE01, N02BE51, N02BE71, N02AA59 and N02AX52) (Table 4).

The other drugs with more than 10% exposure within the 30 days prior to ID are (in descending order of frequency): drugs for treatment of tuberculosis (ATC code J04A) (19.5%), antidepressants (ATC code N06A) (15.9%), direct acting antivirals (ATC code J05A) (14.6%), anxiolytics (ATC code N05B) (13.4%), and antiepileptics (ATC code N03A) (13.4%) (Table 3).

Of the 132 "acute drug overdose" cases of ALFT, most (98.5%) were exposed to paracetamol, plain and combination (ATC codes N02BE01, N02BE51, N02BE71, N02AA59 and N02AX52). Overdose was attributed to paracetamol for 95.5% of the cases, and was considered as non-intentional for 57 (43.2%), and intentional for 69 (52.3%) (Table 4).

The other drugs with more than 10% exposure within the 30 days prior to ID are (in descending order of frequency): anxiolytics (ATC code N05B) (32.6%), antidepressants (ATC code N06A) (22.0%), hypnotics and sedatives (ATC code N05C) (15.2%), NSAIDs (ATC code M01A) (12.1%), and antiepileptics (ATC code N03A) (10.6%) (Table 3).

Table 3. Drug exposure of ALFT cases "without identified clinical cause" within 30 days prior to index date for the 6-year period (2008 to 2013).

	Acute drug overdose n = 132		Exposed to drugs n = 82		Not exposed to drugs n = 32		Total n = 246	
At least one exposure, n (%)								
Other analgesics and antipyretics	127	(96.2)	37	(45.1)			164	(66.7)
Paracetamol	*109*	*(82.6)*	*32*	*(39.0)*			*141*	*(57.3)*
Paracetamol, combinations excl. psycholeptics	*22*	*(16.7)*	*4*	*(4.9)*			*26*	*(10.6)*
Acetylsalicylic acid	*0*	*(0.0)*	*5*	*(6.1)*			*5*	*(2.0)*
Paracetamol, combinations with psycholeptics	*2*	*(1.5)*	*2*	*(2.4)*			*4*	*(1.6)*
Nefopam	*0*	*(0.0)*	*2*	*(2.4)*			*2*	*(0.8)*
Anxiolytics	43	(32.6)	11	(13.4)			54	(22.0)
Antidepressants	29	(22.0)	13	(15.9)			42	(17.1)
Antiepileptics	14	(10.6)	11	(13.4)			25	(10.2)
Hypnotics and sedatives	20	(15.2)	3	(3.7)			23	(9.3)
Opioids	11	(8.3)	3	(3.7)			14	(5.7)
Antipsychotics	*8*	*(6.1)*	2	(2.4)			10	(4.1)
Drugs for treatment of tuberculosis	0	(0.0)	16	(19.5)			16	(6.5)
Direct acting antivirals	1	(0.8)	12	(14.6)			13	(5.3)
Antiinflammatory and antirheumatic products, non-steroids	16	(12.1)	8	(9.8)			24	(9.8)
Ibuprofen	*6*	*(4.5)*	*4*	*(4.9)*			*10*	*(4.1)*
Diclofenac	*2*	*(1.5)*	*0*	*(0.0)*			*2*	*(0.8)*
Ketoprofen	*2*	*(1.5)*	*0*	*(0.0)*			*2*	*(0.8)*
Diclofenac, combinations	*0*	*(0.0)*	*1*	*(1.2)*			*1*	*(0.4)*
Piroxicam	*1*	*(0.8)*	*0*	*(0.0)*			*1*	*(0.4)*
Naproxen	*1*	*(0.8)*	*0*	*(0.0)*			*1*	*(0.4)*
Nimesulide	*0*	*(0.0)*	*1*	*(1.2)*			*1*	*(0.4)*
Celecoxib	*0*	*(0.0)*	*1*	*(1.1)*			*1*	*(0.4)*
Lipid modifying agents, plain	3	(2.3)	8	(9.8)			11	(4.5)
Antithrombotic agents	2	(1.5)	8	(9.8)			10	(4.1)

Table 4. Paracetamol exposure of ALFT cases "without identified clinical cause" according to drug exposure within the 30 days prior to index date for the 6-year period (2008 to 2013).

	Acute drug overdose n = 132	Exposed to drugs n = 82	Not exposed to drugs n = 32	Total n = 246
At least one exposure at paracetamol, n (%)				
Paracetamol, plain and combinations	**130 (98.5)**	**35 (42.7)**	**0 (0.0)**	**165 (67.1)**
Paracetamol	109 (82.6)	32 (39.0)	0 (0.0)	141 (57.3)
Paracetamol, combinations excl. psycholeptics	22 (16.7)	4 (4.9)	0 (0.0)	26 (10.6)
Paracetamol, combinations with psycholeptics	2 (1.5)	2 (2.4)	0 (0.0)	4 (1.6)
Codeine, combinations excl. psycholeptics	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tramadol, combinations	6 (4.5)	0 (0.0)	0 (0.0)	6 (2.4)
At least one overdose, n (%)	**126 (95.5)**	**0 (0.0)**	**0 (0.0)**	**126 (51.2)**
At least one intentional overdose, n (%)	69 (52.3)	0 (0.0)	0 (0.0)	69 (28.0)
At least one non-intentional overdose, n (%)	57 (43.2)	0 (0.0)	0 (0.0)	57 (23.2)

B- Pooled SALT-I/SALT-II (9-year period, 2005-2013)

Of the 347 ALFT cases "without identified clinical cause", about seven out of ten cases (70.3%) were exposed to other analgesics and antipyretics (ATC code N02B), particularly paracetamol: 60.8% of cases exposed to paracetamol without combinations (ATC code N02BE01) (Table 5), and 70% to paracetamol, plain and combination (ATC codes N02BE01, N02BE51, N02BE71, N02AA59 and N02AX52) (Table 6).

Of the 347 cases, two out of ten were exposed to anxiolytics (ATC code N05B) and/or antidepressants (ATC code N06A) (21.9%, and 17.0%, respectively). One case out of ten was exposed to antiepileptics (ATC code N03A), NSAID (ATC code M01A) and/or hypnotics and sedatives (ATC code N05C) (10.4%, 10.4%, and 8.6%, respectively) (Table 5).

Of the 147 drug-exposed ALFT cases, about three out of five (58.5%) were exposed to other analgesics and antipyretics (ATC code N02B), particularly paracetamol: 49.7% of cases exposed to paracetamol without combinations (ATC code N02BE01) (Table 5), and 49.7% to paracetamol, plain and combination (ATC codes N02BE01, N02BE51, N02BE71, N02AA59 and N02AX52) (Table 6).

The other drugs with more than 10% exposure within the 30 days prior to ID are (in descending order of frequency): anxiolytics (ATC code N05B) (13.6%), drugs for treatment of tuberculosis (ATC code J04A) (12.9%), antiepileptics (ATC code N03A) (12.2%), NSAIDs (ATC code M01A) (12.2%), and antidepressants (ATC code N06A) (11.6%).

Of the 164 "acute drug overdose" cases of ALFT, most (98.2%) were exposed to paracetamol, plain and combination (ATC codes N02BE01, N02BE51, N02BE71, N02AA59 and N02AX52). Overdose was attributed to paracetamol for 95.7% of the cases, and was considered as non-intentional for 62 (37.8%), and intentional for 95 (57.9%) (Table 6).

The other drugs with more than 10% exposure within the 30 days prior to ID are (in descending order of frequency): anxiolytics (ATC code N05B) (34.1%), antidepressants (ATC code N06A) (25.6%), hypnotics and sedatives (ATC code N05C) (15.2%), antiepileptics (ATC code N03A) (11.0%), and NSAIDs (ATC code M01A) (11.0%) (Table 5).

Drug exposure frequency for the total of ALFT cases "without identified clinical cause" within 30 days prior to ID remained constant regardless of different study periods (9-years (2005-2013) or 6-years period (2008-2013)). On the other hand, it should be underlined that among the drug-exposed ALFT cases, paracetamol exposed ALFT cases increased for the extended 9-year period when compared to 6-year period (55.8% *versus* 42.7%).

Table 5. Drug exposure of ALFT cases "without identified clinical cause" within 30 days prior to index date for the pooled 9-year period (2005 to 2013).

	Acute drug overdose n = 164	Exposed to drugs n = 147	Not exposed to drugs n = 36	Total n = 347
At least one exposure, n (%)				
Other analgesics and antipyretics	158 (96.3)	86 (58.5)		244 (70.3)
Paracetamol	*138 (84.1)*	*73 (49.7)*		*211 (60.8)*
Paracetamol, combinations excl. psycholeptics	*30 (18.3)*	*13 (8.8)*		*43 (12.4)*
Acetylsalicylic acid	*1 (0.6)*	*11 (7.5)*		*12 (3.5)*
Paracetamol, combinations with psycholeptics	*2 (1.2)*	*2 (1.4)*		*4 (1.2)*
Nefopam	*0 (0.0)*	*2 (1.4)*		*2 (0.6)*
Anxiolytics	56 (34.1)	20 (13.6)		76 (21.9)
Antidepressants	42 (25.6)	17 (11.6)		59 (17.0)
Antiepileptics	18 (11.0)	18 (12.2)		36 (10.4)
Hypnotics and sedatives	25 (15.2)	5 (3.4)		30 (8.6)
Opioids	16 (9.8)	4 (2.7)		20 (5.8)
Antipsychotics	9 (5.5)	5 (3.4)		14 (4.0)
Drugs for treatment of tuberculosis	0 (0.0)	19 (12.9)		19 (5.5)
Beta-lactam antibacterials, penicillins	4 (2.4)	13 (8.8)		17 (4.9)
Direct acting antivirals	1 (0.6)	13 (8.8)		14 (4.0)
Antiinflammatory and antirheumatic products, non-steroids	18 (11.0)	18 (12.2)		36 (10.4)
Ibuprofen	7 (4.3)	8 (5.4)		15 (4.3)
Ketoprofen	2 (1.2)	3 (2.0)		5 (1.4)
Diclofenac	2 (1.2)	1 (0.7)		3 (0.9)
Celecoxib	0 (0.0)	1 (0.7)		1 (0.3)
Diclofenac, combinations	0 (0.0)	1 (0.7)		1 (0.3)
Meloxicam	0 (0.0)	1 (0.7)		1 (0.3)
Naproxen	1 (0.6)	0 (0.0)		1 (0.3)
Niflumic acid	0 (0.0)	1 (0.7)		1 (0.3)
Nimesulide	0 (0.0)	1 (0.7)		1 (0.3)
Piascledine	0 (0.0)	1 (0.7)		1 (0.3)
Piroxicam	1 (0.6)	0 (0.0)		1 (0.3)
Lipid modifying agents, plain	6 (3.7)	11 (7.5)		17 (4.9)
Antithrombotic agents	3 (1.8)	12 (8.2)		15 (4.3)

Table 6. Paracetamol exposure of ALFT cases "without identified clinical cause" according to drug exposure within the 30 days prior to index date for the pooled 9-year period (2005 to 2013).

	Acute drug overdose n = 164	Exposed to drugs n = 147	Not exposed to drugs n = 36	Total n = 347
At least one exposure at paracetamol, n (%)				
Paracetamol, plain and combinations	**161 (98.2)**	**82 (55.8)**	**0 (0.0)**	**243 (70.0)**
Paracetamol	138 (84.1)	73 (49.7)	0 (0.0)	211 (60.8)
Paracetamol, combinations excl. psycholeptics	30 (18.3)	13 (8.8)	0 (0.0)	43 (12.4)
Paracetamol, combinations with psycholeptics	2 (1.2)	2 (1.4)	0 (0.0)	4 (1.2)
Codeine, combinations excl. psycholeptics	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Tramadol, combinations	6 (3.7)	0 (0.0)	0 (0.0)	6 (1.7)
At least one overdose, n (%)	**157 (95.7)**	**0 (0.0)**	**0 (0.0)**	**157 (45.2)**
At least one intentional overdose, n (%)	95 (57.9)	0 (0.0)	0 (0.0)	95 (27.4)
At least one non-intentional overdose, n (%)	62 (37.8)	0 (0.0)	0 (0.0)	62 (17.9)

10.2.2.3 Drug exposure by different time windows

A- SALT-II Study (6-year period, 2008-2013)

The drug exposure of the 246 ALFT cases "without identified clinical cause" varies slightly according to different time windows: 223 cases (90.6%) were exposed to drugs 90 days prior to the index date, 214 (87.0%) cases exposed 30 days prior to the index date, 207 (84.1%) cases exposed 15 days prior to the index date, and 201 (81.7%) cases exposed 7 days prior to the index date (Table 7).

Drug exposure covers all ALFT cases "exposed to drugs" (exposure at therapeutic dose) and cases with "acute drug overdose" (intentional or non-intentional drug overdoses).

Of all 214 drug-exposed cases of ALFT (non-overdose and overdose) 30 days prior to the index date (38.3% of all-cause ALFT cases, and 87.0% of the ALFT cases "without identified clinical cause), 35 (16% of drug-exposed cases) exposures to paracetamol at therapeutic doses were observed. When paracetamol exposures at therapeutic doses and/or non-intentional overdoses were considered together, this increased up to 92 exposures (43% of drug-exposed cases), and when all exposures (therapeutic doses, intentional or non-intentional overdoses) was considered a total of 161 (75.2% of drug-exposed cases) exposures to paracetamol was identified.

The exposure to paracetamol seemed to stay relatively constant by testing different exposure windows of 90-days to 7 days prior to index date. At therapeutic doses, it varied from 39 exposures at 90-days exposure window to 31 exposures at 7-day exposure window; at therapeutic doses and non-intentional overdose, it varied from 96 exposures at 90-days exposure window to 88 exposures at 7-days exposure window; and finally when considering all exposures, it varied from 165 exposures to 157 at 90- and 7-day exposure windows respectively.

Table 7. Stratification of ALFT cases "without identified clinical cause" with drug exposure by different time windows for the 6-year period (2008 to 2013).

Drug	90 days prior to index date (n=223 cases)	30 days prior to index date (n=214 cases)	15 days prior to index date (n=207 cases)	7 days prior to index date (n=201 cases)
Paracetamol *	39	35	35	31
Paracetamol * (with non-intentional overdoses)	96	92	92	88
Paracetamol * (with intentional or non-intentional overdoses)	165	161	161	157
Treatment for tuberculosis	16	16	16	14
Antidepressants	13	13	12	12
Anxiolytics	13	11	10	10
Direct acting antivirals	12	12	12	12
Antiepileptics	12	11	9	7
Antithrombotic agents	10	8	8	8
Lipid modifying agents, plain	8	8	8	7
NSAID	8	8	6	5

* Paracetamol + paracetamol combination

B- Pooled SALT-I/SALT-II (9-year period, 2005-2013)

The drug exposure of the 347 ALFT cases "without identified clinical cause" varied slightly when different exposure windows were considered: 321 cases (92.5%) were exposed to drugs 90 days prior to the index date, 311 (89.6%) cases exposed 30 days prior to the index date, 303 (87.3%) cases exposed 15 days prior to the index date and 296 (85.3%) cases exposed 7 days prior to the index date (Table 8).

Drug exposure covers all ALFT cases "exposed to drugs" (exposure at therapeutic dose) and cases with "acute drug overdose" (intentional or non-intentional drug overdoses).

Of all 311 cases of ALFT identified "with drug exposure" (non-overdose and overdose) 30 days prior to the index date (42.5% of all-cause ALFT cases and 89.6% of the ALFT cases "without identified clinical cause), 82 (26.4%) exposures to paracetamol at therapeutic doses were observed. When paracetamol exposures at therapeutic doses and/or non-intentional overdoses were considered together, this increased up to 144 exposures (46.3%), and when all exposures (therapeutic dose, intentional or non-intentional overdoses) was considered a total of 239 (76.8%) exposures to paracetamol was identified.

The exposure to paracetamol seemed to stay relatively constant by testing different exposure windows of 90-days to 7 days prior to index date. At therapeutic doses, it varied from 86 exposures at 90-day exposure window to 77 exposures at 7-day exposure window; at therapeutic doses and non-intentional overdose, it varied from 148 exposures at 90-day exposure window to 139 exposures at 7-day exposure window; and finally when considering all exposures, it varied from 243 exposures to 234 at 90-day and 7-day exposure windows respectively.

Among all 311 ALFT cases exposed to drugs within 30 days prior to index date, 20 cases (6.4%) were exposed anxiolytics (ATC code N05B), 19 (6.1%) to treatment for tuberculosis (ATC code J04A), 18 (5.8%) to antiepileptics (ATC code N03A) and NSAIDs (ATC code M01A), and 17 (5.5%) to antidepressants (ATC code N06A). These were relatively stable when the other exposure windows were considered.

The incidence of NSAID exposure decreased from 19 for the 90-day exposure window period to 13 for the 7-day exposure window period.

The drug exposure of the ALFT cases seemed to be constant when four exposure windows (at 90, 30,15 and 7 days prior to index date) were tested regardless of the study period (6-year period, 2008-2013 or 9-year period, 2005-2013).

Table 8. Stratification of ALFT cases "without identified clinical cause" with drug exposure by different exposure windows for the pooled 9-year period (2005 to 2013).

Drug	90 days prior to index date (n=321 cases)	30 days prior to index date (n=311 cases)	15 days prior to index date (n=303 cases)	7 days prior to index date (n=296 cases)
Paracetamol *	86	82	81	77
Paracetamol * (with non-intentional overdoses)	148	144	143	139
Paracetamol * (with intentional or non-intentional overdoses)	243	239	238	234
Anxiolytics	22	20	19	19
Antiepileptics	19	18	16	14
NSAID	19	18	14	13
Treatment for tuberculosis	19	19	19	17
Antidepressants	17	17	16	16
Antithrombotic agents	14	12	12	12

* Paracetamol + paracetamol combination

10.3 MAIN RESULTS

10.3.1 Incidence rates of ALFT according to drug exposure within 30 days prior to index date

A- SALT-II Study (6-year period, 2008-2013)

The incidence rates were computed taking into account of the reference population extracted from the EGB database. Drug dispensation was then extrapolated to the whole population.

The selection of the reference population, drug dispensation, total number of DDDs, and the estimation of patient-years exposed to drugs of the extrapolated population for the 6-year period (2008-2013) are presented in Table 10 and 11 of Appendix 1.2.

ALFT incidence rates "per billion DDD", "per billion patients" and "per billion patient-years" for the most frequent drug class exposures 30 days prior index date for the 6-year period (2008-2013) are presented in Table 9.

As presented previously, ALFT cases without identified clinical registered between 2008-2013 for ALFT cause were largely exposed to paracetamol.

ALFT incidence rate for non-overdose paracetamol (at therapeutic dose) was 6.05 (95%CI 4.22; 8.42) case per billion DDD, was 743.87 (95%CI 518.16; 1034.61) case per billion patients (for 6 years), and 222.22 (95%CI 154.79; 309.07) case per billion patient-years.

The incidence rates of ALFT were 2.5 fold higher when cases with non-intentional paracetamol overdose were as well included in the analyses to those exposed at therapeutic doses: 15.91 (95%CI 12.83; 19.51) ALFT cases per billion DDD, or 1955.31 (95%CI 1576.15; 2398.02) ALFT cases per billion patients or 574.11 (95%CI 470.84; 716.36) ALFT cases per billion patients-years.

When all exposures to paracetamol were considered (therapeutic doses, intentional and non-intentional overdoses), ALFT incidence rates continued to increase; 27.84 (95%CI 23.71; 32.50) case per billion DDD, 3421.80 (95%CI 2913.64; 3993.64) case per billion patients, and 1022.19 (95%CI 870.39; 1193.03) case per billion patients-years.

As for SALT-I, the ALFT incidence rates for paracetamol were compared to NSAIDs. As observed in the SALT-I study, the incidence rates of ALFT were lower for NSAIDS than for paracetamol: 1.62 (95%CI 0.70; 3.20) cases per billion DDD, 196.34 (95%CI 84.67; 386.80) cases per billion patients, and 71.66 (95% CI 30.90; 141.18) cases per billion patient-years.

Table 9. Drug-exposed ALFT incidence rates (30-day exposure window) for the 6-year period (2008 to 2013).

Drug	Number of cases exposed to drugs	Number of DDD of drug (extrapolation)	Number of patients exposed to drug (extrapolation)	Number of patient-years exposed to drugs (extrapolation)	Case per billion DDD (for 6 years) [95% CI] [1]	Case per billion patients (for 6 years) [95% CI] [1]	Case per billion patient-years [95% CI] [1]
Paracetamol *	35	5 782 254 449	47 051 322	157 504 366	6.05 [4.22; 8.42]	743.87 [518.16; 1034.61]	222.22 [154.79; 309.07]
Paracetamol * (with non-intentional overdoses)	92	5 782 254 449	47 051 322	157 504 366	15.91 [12.83; 19.51]	1955.31 [1576.15; 2398.02]	584.11 [470.84; 716.36]
Paracetamol * (with intentional or non-intentional overdoses)	161	5 782 254 449	47 051 322	157 504 366	27.84 [23.71; 32.50]	3421.80 [2913.64; 3993.66]	1022.19 [870.39; 1193.03]
Treatment for tuberculosis	16	27 952 617	213 246	253 175	572.40 [327.34; 929.43]	75030.72 [42908.19; 121831.1]	63197.39 [36141.01; 102616.8]
Antidepressants	13	6 011 672 500	11 350 851	29 629 300	2.16 [1.15; 3.70]	1145.29 [609.65; 1958.44]	438.75 [233.55; 750.27]
Direct acting antivirals	12	349 613 819	4 716 428	7 288 365	34.32 [17.73; 59.95]	2544.30 [1314.55; 4444.04]	1646.46 [850.67; 2875.82]
Anxiolytics	11	6 052 094 564	20 331 487	49 143 265	1.82 [0.91; 3.25]	541.03 [270.02; 967.96]	223.84 [111.71; 400.46]
Antiepileptics	11	1 730 360 430	5 577 778	12 528 686	6.36 [3.17; 11.37]	1972.11 [984.26; 3528.29]	877.99 [438.19; 1570.80]
Antithrombotic agents	8	8 137 220 323	7 971 368	27 319 002	0.98 [0.42; 1.94]	1003.59 [432.80; 1977.08]	292.84 [126.29; 576.89]
Lipid modifying agents, plain	8	10 819 673 646	10 607 977	41 436 867	0.74 [0.32; 1.46]	754.15 [325.23; 1485.67]	193.06 [83.26; 380.34]
NSAID	8	4 927 318 292	40 744 642	111 634 392	1.62 [0.70; 3.20]	196.34 [84.67; 386.80]	71.66 [30.90; 141.18]

* Plain and combinations (N02BE01 + N02BE51 + N02BE71 + N02AA59+ N02AX52)
[1] by the Poisson method

B- Pooled SALT-I/SALT-II (9-year period, 2005-2013)

The selection of the reference population, drug dispensation, total number of DDDs, and the estimation of patient-years exposed to paracetamol and NSAIDs of the extrapolated population for the 9-year period (2005-2013) are presented in Table 25 and 26 of Appendix 1.2.

ALFT incidence rates "per billion DDD", "per billion patients" and "per billion patient-years" for cases exposed to paracetamol and NSAIDs 30 days prior index date for the 9-year period (2005-2013) are presented in Table 10.

The incidence rate of ALFT for non-overdose paracetamol (at therapeutic dose) was 10.52 (95%CI 8.37; 13.06) case per billion DDD, 1591.94 (95%CI 1266.18; 1975.95) case per billion patients, and 363.95 (95%CI 289.47; 451.74) case per billion patient-years.

The incidence rates of ALFT were 1.7 fold higher when cases with non-intentional paracetamol overdose were as well included in the analyses to those exposed at therapeutic doses: 18.48 (95%CI 15.58; 21.76) ALFT cases per billion DDD, 2795.61 (95%CI 2357.64; 3291.87) ALFT cases per billion patients, and 639.13 (95%CI 539.00; 752.59) ALFT cases per billion patients-years.

When all exposures to paracetamol were considered (therapeutic doses, intentional and non-intentional overdoses), ALFT incidence rates continued to increase: 30.67 (95%CI 26.90; 34.82) case per billion DDD, 4639.93 (95%CI 4070.32; 5267.48) case per billion patients, and 1060.78 (95%CI 930.56; 1204.25) case per billion patients-years.

ALFT incidence rates were lower for NSAIDs than for paracetamol: 2.45 (95%CI 1.45; 3.87) case per billion DDD, 388.99 (95%CI 230.58; 614.82) case per billion patients, and 108.93 (95% CI 64.57; 172.17) case per billion patient-years.

Table 10. NSAID- and paracetamol-exposed ALFT incidence rates (30-day exposure window) for the pooled 9-year period (2005 to 2013).

Drug	Number of cases exposed to drugs	Number of DDD of drug (extrapolation)	Number of patients exposed to drug (extrapolation)	Number of patient-years exposed to drugs (extrapolation)	Case per billion DDD (for 9 years) [95% CI] [1]	Case per billion patients (for 9 years) [95% CI] [1]	Case per billion patient-years [95% CI] [1]
Paracetamol *	82	7 793 275 520	51 509 379	225 305 549	10.52 [8.37; 13.06]	1591.94 [1266.18; 1975.95]	363.95 [289.47; 451.74]
Paracetamol * (with non-intentional overdoses)	144	7 793 275 520	51 509 379	225 305 549	18.48 [15.58; 21.76]	2795.61 [2357.64; 3291.87]	639.13 [539.00; 752.59]
Paracetamol * (with intentional or non-intentional overdoses)	239	7 793 275 520	51 509 379	225 305 549	30.67 [26.90; 34.82]	4639.93 [4070.32; 5267.48]	1060.78 [930.56; 1204.25]
NSAID	18	7 347 122 957	46 273 864	165 244 508	2.45 [1.45; 3.87]	388.99 [230.58; 614.82]	108.93 [64.57; 172.17]

* Plain and combinations (N02BE01 + N02BE51 + N02BE71 + N02AA59+ N02AX52)
[1] by the Poisson method

10.3.2 Incidence rates of ALFT according to drug exposure within 90-, 15-, and 7-days prior to index date

The results of the incidence rates of ALFT with different exposure windows (90, 15, and 7 days prior to index date) in the 6-year SALT-II study, and in the pooled 9-year SALT-I/SALT-II are presented in Tables 13, 14, 15 and 28, 29, 30 of Appendix 1.2.

10.4 OTHER ANALYSES

Not applicable.

10.5 ADVERSE EVENTS/ADVERSE REACTIONS

Since the study is a non-interventional study, based on secondary use of data, the reporting of suspected adverse reactions was not required.

11 DISCUSSION

11.1 KEY RESULTS

The SALT-II study has exhaustively included all 22 eligible liver transplant centres in France, for all contributed data, proving the feasibility and the operationability of the study at a higher level. Furthermore, pooling of SALT-II data with SALT-I data allowed greater number of ALFT events and therefore a better precision of the risk estimates.

Over the 6-year period (2008-2013), 8 341 patients registered for liver transplantation were included in the SALT-II study (1 390 cases per year). The number of cases registered for transplantation has slightly increased since SALT-I study.

Demographic characteristics of ALFT cases for the pooled 9-year period (2005-2013) stayed similar to the one for the 6-year period (2008-2013), the demographic proportions remained constant regardless the study period.

According to the clinical diagnosis recorded in the CRISTAL database, 559 cases (6.7% of registered cases) were diagnosed with ALFT, which has increased 1.6-fold since SALT-I study when considered as per year (58.6 *versus* 93 cases, respectively for SALT-I and SALT-II).

The main cases were non-overdose drug-exposed ALFT without identified clinical cause, for which SALT-II has identified 82 cases (14.7%) over the 6-year period; this decreased since SALT-I study when considered per year (21.6 *versus* 13.6 cases, respectively for SALT-I and SALT-II).

An important finding of the SALT-II study is that of the 246 drug-exposed ALFT cases without identified clinical cause, 132 (23.6% of ALFT) were acute drug overdose cases. This was more than two-fold increase since SALT-I study when considered per year (10.6 *versus* 22 cases, respectively for SALT-I and SALT-II). The increase in acute overdose ALFT cases worth pay attention, and the reasons behind should better be further evaluated.

When data were pooled for the pooled 9-year period (2005-2013), non-overdose drug-exposed ALFT cases frequency was 16.3 cases. However, acute drug overdose cases remained increased since SALT-I study; 18.2 cases per year. When non-overdose paracetamol-exposed ALFT cases were evaluated, the increase was obvious for the pooled 9-year period when compared to 6-year period SALT-II (55.8% *versus* 42.7%).

Paracetamol is a drug known to be hepatotoxic by a direct mechanism related to a toxic metabolite that is normally neutralized by glutathione. Paracetamol becomes hepatotoxic when glutathione is depleted, such as in the case of overdose whether voluntary or inadvertent, or with chronic alcoholism or malnutrition.

Acute drug overdose, especially with paracetamol, may cause ALFT. Population statistics and between-country differences for ALFT related to overdose have been poorly described. The 7-country 3-year SALT-I study has evaluated ALFT cases of overdose, (17) and concluded that paracetamol overdose was found to represent one-sixth of all-cause ALFT, and there was a 50-fold difference in Europe in the rates of paracetamol overdose ALFT, and a 200-fold difference per million inhabitants. What SALT-I has added to already known was that paracetamol overdose, even without suicidal intent, represents a large proportion of ALFT, and the frequency of paracetamol overdose leading to ALFT varies considerably between countries, whether per ton of paracetamol sold or by number of inhabitants. Considering all 7 countries, most overdoses (63.0%) were intentional (suicide attempts); intentionality was uncertain in 28%. Overdose was responsible for 19.0% of all-cause ALFT in the seven participating countries. This was highest in Ireland (52.0%), followed by the UK (28.0%), France (18.0%), the Netherlands (8.0%) and Italy (1.0%). Precisely, France had the highest per capita use of paracetamol but the third lowest ALFT rate, as SALT-I study determined. These results are more relevant considering that paracetamol would be the alternate choice for NSAIDs, and is recommended as first-line treatment for the alleviation of pain especially for chronic painful disorders such as osteoarthritis, one of the main indications for NSAIDs, and non-treatment is often not an option in these painful patients.

In SALT-I, a number of cases were identified where the hepatotoxicity occurred after inadvertent overdose, or even after normal usage. The event rates for paracetamol found within 30 days before onset of symptoms, excluding voluntary overdoses was 11 per million treatment-years or 14.45 per billion DDD, *i.e.* an event rate at least twice or three times the event rates observed with most individual NSAIDs or all NSAIDs pooled. Because paracetamol is often used OTC and may not have been registered or reported in medical files, thus, event rates may be higher still. Regardless of this point of view, SALT-II study identified significant and important results concerning paracetamol, like SALT-I. In the 6-year period SALT-II study, similar picture has continued; most (98.5%) acute drug overdose cases of ALFT were exposed to paracetamol, overdose was attributed to paracetamol for 95.5% of the cases, and was considered as non-intentional for 57 (43.2%), and intentional for 69 (52.3%). When SALT-I/SALT-II pooled, results remained consistent; 98.2% of acute overdose ALFT cases were exposed to paracetamol, overdose was attributed to paracetamol for 95.7% of the cases, and was considered as non-intentional for 62 (37.8%), and intentional for 95 (57.9%). Furthermore, the incidence rates of ALFT were 2.5 fold higher when cases with non-intentional paracetamol overdose were as well included in the analyses to those exposed at therapeutic doses. When all exposures to paracetamol were considered (therapeutic doses, intentional and non-intentional overdoses), ALFT incidence rates continued to increase. Pooled SALT-I/SALT-II estimated increased incidence rates of paracetamol-exposed ALFT, indicating that there is an important problem of paracetamol overdose leading to ALFT in France, and reasons behind should be further evaluated.

On the other hand, when testing different exposure windows in SALT-II, paracetamol exposure seemed to stay relatively constant. At therapeutic doses, it varied from 39 exposures at 90-days exposure window to 31 exposures at 7-day exposure window; at therapeutic doses and non-intentional overdose, it varied from 96 exposures at 90-days exposure window to 88 exposures at 7-days exposure window; and finally when considering all exposures, it varied from 165 exposures to 157 at 90- and 7-day exposure windows respectively.

Another interesting finding of SALT-II study, as it focused on all drugs different than SALT-I study, was that the exposure to drugs for treatment for tuberculosis (ATC code J04A), antidepressants (ATC code N06A), direct acting antivirals (ATC code J05A), anxiolytics (ATC code N05B) or antiepileptics (ATC code N03A). These proportions stayed were relatively stable when the other exposure windows were considered. When data were pooled for the 9-year period, the most frequent drug classes of exposure were anxiolytics, drugs for treatment for tuberculosis, antiepileptics, NSAIDs, antidepressants. The incidence rates of ALFT for cases

exposed to drugs for treatment for tuberculosis (ATC code J04A), antidepressants (ATC code N06A), direct acting antivirals (ATC code J05A), anxiolytics (ATC code N05B) or antiepileptics (ATC code N03A) have not been evaluated in SALT-I, as SALT-I focused on only NSAIDs and paracetamol. These findings of high incidence rates found in SALT-II need to be further evaluated in complementary data analyses.

The number of exposure to NSAIDs decreased from eight for the 90-days exposure window period to five for the 7-days exposure window period. Considering the very small number of cases with NSAIDs, it was difficult to identify any risk factors or differences in hepatic diseases between different NSAIDs. A certainty is that most cases were also exposed to other drugs, especially paracetamol, within the 30-day period before the first clinical symptoms. In the 6-year SALT-II study, the number of exposure to NSAIDs decreased from eight for the 90-days exposure window period to five for the 7-days exposure window period. As done for SALT-I, the ALFT incidence rates for paracetamol were compared to NSAIDs. As observed in the SALT-I study, the incidence rates of ALFT were lower for NSAIDS than for paracetamol in 6-year SALT-II, and when data were pooled for 9-years SALT-I/SALT-II, ALFT incidence rates were still lower for NSAIDs than for paracetamol.

In the SALT-I study, population exposure was computed from the Intercontinental Medical Services' (IMS) to compute homogeneous population exposure data source for all seven participating countries, including France. While performing data analyses for SALT-II as well as pooled SALT-I/SALT-II, the French national healthcare insurance system's database, EGB, was used, so that the results could be comprehensible. If to present briefly EGB database, it is a 1/97 representative sample of persons included in the anonymized national healthcare insurance information systems data- base (SNIIR-AM). This source database covers between 80% and 85% of the French population, and the conversion ratio to extrapolate from the EGB to the national population is calculated every year, adjusted to the age structure of the population, the national coverage of the parent database, and the sampling ratio. EGB contains all individual medical expenses covered by the insurance system, including all reimbursed drug dispensations, with identification of medication packs, including the number and strength of tablets. This provides dispensation patterns and quantities and the number of patients exposed to individual drugs or drug classes, as well as the dates of prescription and dispensation. (16)

11.2 BIAS

Selection bias is unlikely to be influential in this study for several reasons: Firstly, all liver transplant centres in France participated and contributed data to the study. Patients included in the study were residents where they were registered for transplantation.

Bias on population exposure data is also unlikely, as the use of EGB database in pharmacoepidemiological studies and the generalizability of data to entire population have been studied and shown adequate. (18) Furthermore, OTC purchases is not a problem for France as there is a monopoly of distribution.

11.3 STRENGTHS AND LIMITATIONS

The main strength of SALT-II study is that it focused on drug-associated ALFT, whether the patient was transplanted or not, providing an estimate of absolute population-based ALFT event rates independent of causality assessments or spontaneous reporting.

The study succeeded again, like SALT-I study, in the exhaustive participation and data contribution of French liver transplant centres, which provided the inclusion of the target cases (ALFT), per-country identification of cases could therefore be complete which is a prerequisite for a case-population approach. Furthermore, the network of drug-exposed liver injury leading to transplantation (developed by the SALT-I study) has been extended for another six-year period (2008-2013) for a total of nine years (2005-2013), and evaluated all drugs.

The main study design was case-population design, which is appropriate for very rare easily identifiable outcomes for all cases exposed and compared to use of drugs in a defined area (country, region). Risk estimates were based on validated data; using transplant lists included only cases with verified clinical ALF diagnosis, and an expert hepatologist validated collected data.

The last but not the least, the practical organisation of the network as well as the results of the SALT-II study helped and provided necessary scientific and organisation preparations for the prospective study, SALT-III, which has already started and ongoing smoothly in France.

On the other hand, the SALT-II study had some limitations. It had a retrospective design, using pre-existing data, therefore the nature and the quality of which might vary. The study lacked of systematic drug exposure data, and information about the possible concomitant risk factors other than basic items such as age and gender, which might have limited the possibility of identifying the putative high-risk groups. Since it followed the same design as of SALT-I except causality assessments, it could not evaluate risk estimations of drug-exposed ALFT cases with identified clinical cause (whether a drug/drug class caused or aggravated ALFT). However, the ongoing prospective SALT-III study, as well as the new exhaustive EURO-SALT project which is in preparation of set-up, will evaluate all-cause ALFT cases in terms of drug-exposure, which will hopefully provide outcomes for both ALFT cases with or without identified clinical cause.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

SALT-II study results show that acute liver failure leading to transplantation in drug-exposed patients is a rare but important event. Paracetamol exposure at therapeutic doses or at overdose is still the almost exclusive cause for liver transplantation, and has increased in France since SALT-I study period. The reasons for this needs to be further evaluated.

The high incidence rates of ALFT for cases exposed to drugs for treatment for tuberculosis, antidepressants, direct acting antivirals, anxiolytics or antiepileptics need to be further evaluated in complementary data analyses.

The results of both SALT-II study and pooled SALT/SALT-II helped and provided necessary scientific and organisation preparations for the prospective study, SALT-III, which has already started and ongoing smoothly in France. SALT-III study will eventually provide a better profile and better risk estimations and usage patterns for drug-exposed ALFT, and particularly paracetamol-associated overdoses leading to registration for liver transplantation, as the study will be as well evaluating pharmacogenetic factors for drug-associated ALFT.

An outcome not be neglected is also that this study strengthen the key research network of the French liver transplant centres, and showed again the feasibility of networking. The wealth of information and results could thus be worth to help the regulatory authorities for decision-making.

The future perspective is to extend both SALT-II and SALT-III in Europe. A new project named EURO-SALT is under preparation, for which ANSM has expressed its interest, and financed a feasibility study, EURO-SALT(f), scheduled for 2016. The new methods to be developed in EURO-SALT are use of hospital information systems to store and extract case data, systematic retrieval of blood samples for pharmacokinetic, toxicological and pharmacogenetic evaluation of drug hepatotoxicity, identifying possible co-factors or drugs that might worsen the prognosis or outcome of the initial liver injury. Linking to claims databases could provide more exposure information. This is a novel issue that has not been yet studied systematically.

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APPENDICES

APPENDIX 1. LIST OF STAND-ALONE DOCUMENTS

Number	Document reference number	Date	Title
1.1			Study Protocol
1.2			Statistical Analysis Report

APPENDIX 2. ADDITIONAL INFORMATION

Not applicable