Emerging patterns in the development of medicines in paediatric oncology

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BENJAMIN MICALLEF

Department of Pharmacy

University of Malta

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Abstract

Understanding how paediatric oncology medicinal products are developed may facilitate the approval of safe and effective medicines to treat children with cancer.

The aim of this project was to review clinical development programs (CDPs) of medicinal products for acute lymphoblastic leukaemia (ALL) to identify emerging patterns in the development of medicines in paediatric oncology.

CDPs for medicinal products approved in Europe through the centralised procedure to treat ALL in children were retrieved from European public assessment reports (EPARs) of the European Medicines Agency (EMA). CDPs for drugs in the development phase were retrieved from the EMA Paediatric Investigation Plans and from clinical trials registered in the EU clinical trial register and the United States national library of medicine database of clinical trials. Prospective treatment protocols for paediatric ALL were proposed to understand the potential impact that drugs in the development phase could have on clinical practice. The drug category and line of therapy was described for each authorised and prospective product. CDPs were analysed and compared based on the number, type and design of studies, and the endpoints used.

Nine products (7 small molecules and 2 biologicals) were granted marketing authorisations under the centralised procedure to treat paediatric ALL. Three out of the 9 products authorised were new active substances and 6 were based on known active substances. Known active substances included PEGylated asparaginase and intravenous busulfan (new formulation) and oral liquids of methotrexate and mercaptopurine (paediatric friendly dosage forms). The 9 authorised products used 4 different types of marketing authorisation applications: (i) full applications (3 products), (ii) well-established use applications (2 products), (iii) hybrid medicinal product applications (2 products) and (iv) marketing authorisations under exceptional circumstance (2 products). The CDPs supporting the

authorisation of products varied from extensive (10 adult trials, 2 paediatric studies and 1 pharmacokinetic modelling study) for products applying for first line indications through full applications to minimal (1 adult and 1 paediatric trial) for products seeking third line indications under exceptional circumstances. Thirty-five prospective products are in phase II and phase III development: small molecules (17 products including 2 novel liposomal formulations), advanced therapy medicinal products (9 ATMPs), biologicals (7 products including 2 novel PEGylated or erythrocyte-encapsulated formulations) and antibody drug conjugates (2 products). Drugs in the development phase will not significantly alter first line ALL treatment protocols in children. Prospective products for *de novo* ALL will likely be used as add-on therapies to the chemotherapeutic backbone established in past large-scale trials. Monotherapy with biologicals, antibody drug conjugates or chimeric antigen receptor T-cell based ATMPs is being explored as a strategy to improve cure rates in relapsed or refractory paediatric ALL.

Based on emerging patterns observed, this study suggests that companies are using 2 strategies to bring products for paediatric ALL to market: (i) Companies develop new formulations of the established products, such as liposomal, PEGylated or paediatric friendly dosage forms, as a drug development strategy to overcome acute toxicities, improve patient safety and promote treatment compliance, (ii) Companies that develop new active substances target niche (narrow) indications where there is an unmet medical need and may later extend indications through post-authorisation procedures supported by clinical trials in appropriately selected patient cohorts.

Keywords

Clinical development programs, paediatric oncology, trends in drug development, acute lymphoblastic leukaemia, prospective treatment protocols, medicines for children

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Glossary

Term	Definition	Reference
Acute lymphoblastic leukaemia (ALL)	A malignant disorder of lymphoid progenitor cells that affects both children and adults with peak prevalence between the ages of 2 and 5 years	Pui et al, 2008
Allocation	A method used to assign participants to an arm of a clinical study. The types of allocation are randomized allocation and nonrandomized.	Kalish & Begg, 1985
Complete response/remission (CR)	No evidence of disease, full restoration of normal haematopoiesis and a blast cell fraction of less than 5% determined by light microscopic examination of the bone marrow	Pui & Campana, 2000
Controlled clinical trial	A clinical study that includes a comparison or control group. The comparison group can receive a placebo as is the case in "placebo-controlled trials" or an intervention/treatment considered to be effective as is the case in "active-controlled trials". The control group can also be based on “historical controls” that are derived from published case series or from past trials that established the efficacy of standard therapies	Umscheid et al, 2011, Tsong & Zhang, 2013
Disease-free survival (DFS)	Time from randomisation to recurrence or death from any cause	Bonnetain et al, 2014
Event-free survival (EFS) in leukaemia	Time between study entry and the earliest specified event. In the treatment of acute leukaemia, lack of achievement of CR, relapse and death without relapse are counted as events in an EFS analysis. Those patients who did not reach CR during the pre-specified induction phase are considered as having an event at time 0	Committee for Medicinal Products for Human Use (CHMP), 2017[1]

[1] Committee for Medicinal Products for Human Use. Guideline on the evaluation of anticancer medicinal products in man - EMA/CHMP/205/95 Rev.5 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2017 Sep 22; cited 2017 Jan 10]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/11/WC500238764.pdf

Term	Definition	Reference
Intervention model	The structural designs of a clinical trial that refers to the strategy for assigning interventions to participants. Types of intervention models include: *Single group assignment* - A clinical trial with a single arm where participants are given the experimental treatment and then followed over time to observe their response *Parallel assignment* - A clinical trial with 2 treatment arms where participants in first group receive one treatment and the second group receives another treatment for the total duration of the trial *Cross-over assignment* - A clinical trial where each participant is randomized to a sequence of treatments that will be sequentially administered during treatment periods *Factorial assignment* - A clinical trial studying the effect of two or more interventions that applied alone or in combination	Evans, 2010
Masking or blinding	The process of keeping the study group assignment hidden after allocation that is commonly used to reduce the risk of bias in clinical trials with two or more study groups	Hrobjartsson & Gotzsche, 2010; Hrobjartsson et al, 2012
Minimal residual disease (MRD)	Low-level residual leukemic disease after suboptimal induction chemotherapy. May also be used to refer to the lowest levels of disease potentially compatible with cure or to molecularly defined relapse after long-term remission	Paietta, 2002
Objective response rate (ORR)	The proportion of patients in whom a complete response or partial response was observed	Food and Drug Administration 2007[2], CHMP 2017[1]
Open label or non-masked or unblinded	A type of study in which both the investigator and the patients are not blinded to the treatment allocation and are therefore aware of the drug or treatment being given	Sedgwick, 2014

[1] Committee for Medicinal Products for Human Use. Guideline on the evaluation of anticancer medicinal products in man - EMA/CHMP/205/95 Rev.5 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2017 Sep 22; cited 2017 Jan 10]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2017/11/WC500238764.pdf

[2] Food and Drug Administration. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [Online]. Rockville (MD): U.S. Department of Health and Human Services; c2007 [updated 2007 May 01; cited 2017 Jan 10]. Available from URL: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

Term	Definition	Reference
Overall survival (OS)	Time from randomisation to death from any cause	FDA 2007[2], EMA 2017[1]
Paediatric investigation plan (PIP)	A development plan aimed at ensuring that the necessary data are obtained to support the authorisation of a medicine for children, through studies in children. All applications for marketing authorisation for new medicines must include the results of studies as described in an agreed paediatric investigation plan, unless the medicine is exempt because of a deferral or waiver	European Medicines Agency 2017[3]
Paediatric off-label use	All paediatric uses of a marketed drug not detailed in the SPC with particular reference to; therapeutic indication, therapeutic indication for use in subsets, appropriate strength (dosage by age), pharmaceutical form and route of administration	Neubert et al, 2008
Progression free Survival (PFS)	Time from randomisation to objective tumour progression or death from any cause	Villaruz & Socinski, 2013
Time to Progression (TTP)	Time from randomization until objective tumour progression; Time to Progression does not include deaths	FDA 2007[2]

[2] Food and Drug Administration. Guidance for Industry Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics [Online]. Rockville (MD): U.S. Department of Health and Human Services; c2007 [updated 2007 May 01; cited 2017 Jan 10]. Available from URL: https://www.fda.gov/downloads/Drugs/Guidances/ucm071590.pdf

[3] European Medicines Agency. Paediatric investigation plans [Online]. London (UK): European Medicines Agency; c1995-2017 [cited 2017 Jan 10]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000608.jsp&mid=WC0b01ac0580925b1b

List of Abbreviations

6MP	Mercaptopurine
6TG	Tioguanine
ADC	Antibody-drug conjugate
AE	Adverse event
aGVHD	Acute Graft versus Host Disease
AIFA	Agenzia Italiana del Farmaco
ALL	Acute Lymphoblastic Leukaemia
ANC	Absolute neutrophil count
ara-CTP	Arabinofuranosylcytosine triphosphate
ATC	Anatomical Therapeutic Chemical
ATIMP	Advanced Therapy Investigational Medicinal Product
ATMP	Advanced Therapy Medicinal Product
AUC	Area under the plasma drug concentration-time curve
B-ALL	B-cell lymphoblastic leukaemia
Bcl-2	B-cell lymphoma 2
Bcl-xL	B-cell lymphoma-extra large
BE	Bioequivalence
BiTE	Bispecific T engager
BNFC	British National Formulary for Children
CAP	Centrally Authorised Product
CAR-T	Chimeric Antigen Receptor T Cells
CDP	Clinical Development Program
cGVHD	Chronic Graft versus Host Disease
CHMP	Committee for Human Medicinal Products
Cmax	Maximum (or peak) serum concentration of a drug
CML	Chronic Myeloid Leukaemia
CNS	Central Nervous System
CR	Complete Remission
CSF	Cerebrospinal fluid
DFS	Disease-free survival
DLBCL	Diffuse large B-cell lymphoma
DLT	Dose limiting toxicities
DNA	Deoxyribonucleic acid
E.g	E*xempli gratia*
EBV	Epstein-Barr Virus
EC	European Commission
EEA	European Economic Area
EFS	Event-free survival
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
FAB	French-American-British
FDA	Food and Drug Administration
FLAG	Fludarabine, cytarabine, and granulocyte colony-stimulating factor
GVHD	Graft versus Host Disease

HCL	Hairy Cell Leukaemia
HR	High Risk
HSCT	Haematopoietic stem cell transplantation
IMP	Investigational Medicinal Product
IT	Intratracheal
JAK	Janus Kinases
LBL	Lymphoblastic lymphoma
MA	Marketing Authorisation
MM-TK	MolMED-Thymidine kinase
MRD	Minimal Residual Disease
MSC	Mesenchymal stem cells
MTD	Maximum Tolerated Dose
MTX	Methotrexate
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NRM	Non- relapse mortality
ORR	Overall Remission Rate
OS	Overall Survival
PBPK model	Physiologically-based pharmacokinetic model
PD	Pharmacodynamic
PDCO	Paediatric Committee
PFS	Progression free survival
Ph-	Philadelphia chromosome Negative
Ph+	Philadelphia chromosome Positive
PIP	Paediatric Investigation Plan
PK	Pharmacokinetic
r/r	Relapsed or refractory
RCT	Randomised Controlled Trial
RNA	Ribonucleic acid
SmPC	Summary of Product Characteristics
SR	Standard Risk
T1/2	Biological half-life
T-ALL	T-cell lymphoblastic leukaemia
TBI	Total Body Irradiation
T-LBL	T-cell lymphoblastic lymphoma
Tmax	Time after administration of a drug when Cmax is reached
TRM	Transplant Related Mortality
TTP	Time to progression
UCB	Umbilical Cord Blood
UCL	University Collage London
USAN	United States Approved Name
VSLI	Vincristine Sulfate Liposome Injection
WHO	World Health Organisation
λz	Terminal elimination rate constant

Chapter 1
Introduction

1.1 Background

Cancer describes a collection of related diseases caused by genetic mutations and characterised by uncontrolled cellular proliferation (You & Jones, 2012; Vazquez et al, 2016). The biological process of carcinogenesis is complex and genetics, epigenetics and communication among tumour cells play a role in the modern molecular understanding of cancer (Grizzi et al, 2006; Baylin & Jones, 2011; Sandoval & Esteller, 2012; Tabassum & Polyak, 2015; Pierotti, 2017)

The paediatric patient cohort differs from adults in a number of ways[4] including body composition, organ maturation and physiology (Turner et al, 2014). The paediatric population itself is not homogenous and varies significantly as the child continues to grow and develop (Ernest et al, 2007; Lu & Rosenbaum, 2014; Swain, 2014). These differences have implications on cancer pathogenesis, cancer treatment and drug development in children.

1.1.1 Paediatric Cancer Epidemiology

Cancer in children is rare when compared to cancer in adults (Gatta et al, 2009). In Europe there are about 35000 new cancer cases reported each year for children and adolescents aged between 0 and 24 years (Vassal et al, 2016). Most European countries have an annual paediatric cancer incidence rate in range of 140-160 new cases per million (Kowalczyk et al, 2016). In Malta the Directorate for Health Information and

[4] Commission of the European Communities (EC). Proposal for a Regulation of the European parliament and of the Councilon medicinal products for paediatric use and amending Council Regulation (EEC) No 1786/92, Directive 2001/83/EC and Regulation (EC) No 726/2004: Extended Impact Assessment [Online]. Brussels (BE): Commission Staff Working Document; 2004 [cited 2017 Jan 09]. Available from: http://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2004/sec_2004_1144_en.pdf

Research maintains a national cancer register[5]. The average number of new cancer cases reported in Malta for children aged between 0-19 years is 18 cases per year[6] or about 206 new cases per million (Kowalczyk et al, 2016).

Cancer affects children under 15 years of age, adolescents and young adults and older adults differently (Ferrari et al, 2008; Tricoli et al, 2016). Important differences include the types of cancers developed, therapeutic outcomes and underlying tumour biologies (Bleyer et al, 2008). Young children tend to develop embryonal, small round-cell tumours and haematological malignancies while adults tend to develop epithelial malignancies (Bleyer et al, 2008).

In Europe and North America, leukaemia accounts for 29-34% of all malignancies diagnosed in children under 15 years old, while brain and central nervous system (CNS) tumours and lymphomas account for 26% and 11% of diagnoses respectively (Belson et al, 2007; Arora et al, 2009; Kaatsch, 2010; Kaatsch, 2010; Monaco & Teot, 2014; Bonaventure et al, 2017; Siegel et al, 2017; Siegel et al, 2017). In adolescents (aged 15-19 years) lymphoma is the largest diagnostic group representing 21% of all cases (Siegel et al, 2017). Cancers of the brain and central nervous system (CNS) account for 17% of adolescent cancer cases and leukaemia accounts for 14%.

When children are taken as a whole (ages 0-18 years), acute lymphoblastic leukaemia (ALL) represents 26% of childhood malignancy and contributes to 76-80% of all childhood leukaemia (Kaatsch, 2010; Saletta et al, 2014a; Ward et al, 2014;

[5] Government of Malta. Health Information and Research: Registries [Online]. Valletta (MT): Government of Malta; 2017 [cited 2017 Jan 09]. Available from URL https://health.gov.mt/en/dhir/Pages/Introduction.aspx
[6] Department of Health Information and Research. Malta National Cancer Registry: All Malignant Cancers (Online). Pietà (MT): Department of Health Information and Research; 2017 [cited 2017 Aug 15]. Available from URL https://health.gov.mt/en/dhir/Documents/Cancer/Cancer%20Docs%20July%202017/All%20Cancers_2015.pdf

Bonaventure et al, 2017). Other cancers encountered in children are neuroblastomas and peripheral nervous system tumours, renal tumours, hepatic tumours, soft-tissue sarcomas such as rhabdomyosarcoma, and malignant bone tumours amongst others (Ferrari et al, 2008)

1.1.2 Paediatric Cancer Survival Rates and Treatment Modalities

Cancer survival rates in children have been improved considerably in the past fifty years (Gatta et al, 2005; Gatta et al, 2014; Israels et al, 2015; Fernandez-Delgado, 2016; Ribeiro et al, 2016). This improvement is illustrated by diseases such as acute lymphoblastic leukaemia, non-Hodgkin lymphoma and Wilm's tumour where appropriately treated patients can expect an overall survival rate of over 80% (Gatta et al, 2009; Saletta et al, 2014a; Smith et al, 2014).

The successful treatment of cancer in children with chemotherapeutic agents originally developed for adults has contributed to the rise in cure rates (Paolucci et al, 2008; Adamson, 2015; Rose & Walson, 2015). Chemotherapy was first used in the 1940's, when two prominent pharmacologists used a nitrogen mustard to treat non-Hodgkin's Lymphoma (Papac, 2001). The discovery of the antifolates and purine analogues followed shortly afterwards (DeVita & Chu, 2008; Visentin et al, 2012)). Since then the advent of multi-drug combination chemotherapy regimens has been recognised as a major milestone in cancer treatment (Chabner & Roberts, 2005). The goal of combination therapy based on drugs with non-overlapping mechanisms of action is to attain therapeutic synergism and avoid the emergence of drug resistance (Crawford, 2013; Yardley, 2013). The recent use of targeted immunotherapeutic agents alone or integrated into regimens based on cytotoxic drugs has also advanced the treatment of

cancer (Burney, 2017; Dempke et al, 2017). Other factors such as improvements in the genomic understanding of cancer, diagnostic technologies and supportive care have further enhanced patient survival (Vucic et al, 2012; Biemar & Foti, 2013). Radiation therapy and surgery have been used successfully alongside chemotherapeutic agents and remain valuable treatment options (Sudhakar, 2009; Baskar et al, 2012). Innovative cancer treatments using nanotechnology and gene modified T cells expressing chimeric antigen receptors could potentially enter mainstream cancer therapy in the future (Ferrari, 2005; Jaspers & Brentjens, 2017).

1.1.3 Present Perspective and Challenges in Paediatric Oncology

In spite of the overall progress made, challenges and opportunities persist in the field of paediatric oncology. Paediatric cancer remains a significant public health concern and is the principle cause of non-accidental mortality among children in affluent countries (Gupta et al, 2014; Saletta et al, 2014b; Kowalczyk et al, 2016).

Not all paediatric cancers have achieved high cure rates (Fernandez-Delgado, 2016). For example, intrinsic pontine glioma and metastatic Ewing's sarcomas maintain a poor prognosis of less than 5% and 30% respectively (Miser et al, 2004; MacDonald et al, 2011; Pui et al, 2011; Fangusaro, 2012). Even in malignancies with a high chance of cure such as acute lymphoblastic leukaemia, a fraction of patients is refractory to current treatment while others experience relapse after successful treatment (Schrappe et al, 2012; Davila et al, 2014; Karantanos et al, 2017). Cancer resistance to chemotherapeutics is recognised as one of the limitation of current treatment (Holohan et al, 2013; Zahreddine & Borden, 2013). Tumour resistance is not limited to traditional chemotherapy and has been reported in newer molecularly targeted therapies such as

imatinib and other second-generation tyrosine kinases (Milojkovic & Apperley, 2009; Lee & Chung, 2011; Chang et al, 2012).

Current paediatric cancer treatment, albeit being efficacious and mostly successful, has serious drug-induced toxicities (Ramirez et al, 2009; Ness et al, 2011). Toxicities may present acutely or may emerge later in life as so called late effects that are observed in paediatric cancer survivors (Dickerman, 2007; Oeffinger & Robison, 2007; Nandagopal et al, 2008; Landier et al, 2015; Rose et al, 2016).

Cancer causes direct physical and psychological strain on children and their caregivers and is also a growing financial burden for payers whether the treatment is paid for out-of-pocket by families or funded by national health services (Zafar & Abernethy, 2013; Woźniak & Iżycki, 2014; Warner et al, 2015; Laudicella et al, 2016). Emerging research suggesting that new oncology drugs may not always offer clinically meaningful outcomes may compound the distress associated with the cost of cancer care experienced by patients and their families (Markman & Luce, 2010; Davis et al, 2017).

Cure rates, toxicities and treatment costs motivate the industry, academics and learned societies to sustain research in paediatric oncology, particularly in bringing to the market innovative treatments which are more efficacious and safer.

1.2 Developing Medicines for Children

In the era of data driven and evidence-based medical decision making developing medicines for children is not straightforward (Rose, 2017). The results of tests of

medicines in adults cannot necessarily be extrapolated directly to children[7] because of the inherent differences in body composition, organ maturation and physiology between children and adults (Hirschfeld et al, 2000; Fernandez et al, 2011; Ferro, 2015; Rodieux et al, 2015). It is for this reason that specific research, including pre-clinical studies in juvenile animals[8] as well as PK/PD studies are normally required to ensure the safe and effective use of medicines across all paediatric age groups[9] (Batchelor & Marriott, 2015). Doses and formulations must be adapted to the needs of the paediatric population, for example a solution, syrup, or injection may need to be developed where conventional tablets and capsules are not practical[10](Lehmann, 2008; Rocchi et al, 2010; Turner et al, 2014).

Ethical, technical and logistical difficulties are associated with studying medicines in children (Conroy et al, 2000; Laventhal et al, 2012; Joseph et al, 2016). As the child grows, mental, linear and reproductive development takes place and any possible effects that investigational drug therapy may have during this time must be considered (Bavdekar, 2013; Joseph et al, 2015).

[7] Commission of the European Communities (EC). Proposal for a Regulation of the European parliament and of the Councilon medicinal products for paediatric use and amending Council Regulation (EEC) No 1786/92, Directive 2001/83/EC and Regulation (EC) No 726/2004: Extended Impact Assessment [Online]. Brussels (BE): Commission Staff Working Document; 2004 [cited 2017 Jan 09]. Available from: http://ec.europa.eu/smart-regulation/impact/ia_carried_out/docs/ia_2004/sec_2004_1144_en.pdf

[8] European Medicines Agency (EMA). Guideline on the Need for Non-Clinical Testing in Juvenile Animals of Pharmaceuticals for Paediatric Indications: EMEA/CHMP/SWP/169215/2005 [Online]. London (UK): Committee for Human Medicinal Products (CHMP); 2008 [cited 2017 Jan 09]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003305.pdf

[9] International Conference on Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH). ICH Harmonised Tripartite Guideline: Clinical Investigation of Medicinal Products in the Pediatric Population E11 [Online]. Geneva (CH): ICH; 2000 [cited 2017 Jan 09]. Available from: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E11/ICH_E11_R1_Step_2_25Aug2016_Final.pdf

[10] European Medicines Agency. Reflection Paper: Formulations of Choice for the Paediatric Population: EMEA/CHMP/PEG/194810/2005 [Online]. London (UK): Committee for Human Medicinal Products (CHMP); 2006 [cited 2017 Jan 09]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003782.pdf

Market forces alone had proved to be insufficient to surmount the obstacles associated with conducting trials in children and to stimulate adequate research into paediatric drug development[11]. Prescribers use drugs off-label in clinical practice for lack of alternatives but at the same time the potential detrimental effects that off-label use has on patients and the concerns and challenges of healthcare professionals and industry are acknowledged (Conroy et al, 2003; Casali & Executive Committee of ESMO, 2007; Waller, 2007; Leveque, 2008; Bellis et al, 2013; Lenk & Duttge, 2014; Ellul et al, 2016).

The regulatory regions of the United States and Europe have enacted legislations to stimulate paediatric drug development in attempt to remedy the lack of suitable authorised medicinal products to treat paediatric conditions (Auby, 2008; Zisowsky et al, 2010; Turner et al, 2014; Ceci et al, 2015). In spite of the legal provisions in place and for different reasons, off-label use of medicines in paediatric cancer patients remains prevalent[12] (Roila et al, 2009; van den Berg & Tak, 2011; Lerose et al, 2012; Pfister, 2012) and will likely remain so in coming years (Corny et al, 2015). This highlights the need for evidence-based information on off-label use being made available to oncologists and clinicians in general.

Outside specialised centres, information sources that help clinicians prescribe medicines off-label for children in a safe and effective manner are scarce. Two examples are, the

[11] The European Parliament and the Council of the European Union. REGULATION (EC) No 1901/2006 of THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 12 December 2006 on medicinal products for paediatric use and amending Regulation (EEC) No 1768/92, Directive 2001/20/EC, Directive 2001/83/EC and Regulation (EC) No 726/2004. OJ. 2006;L378:1-19

[12] Weda M, Hoebert J, Vervloet M, Moltó Puigmarti C, Damen N, Marchange S, et al. Study on off-label use of medicinal products in the European Union [Online]. Brussels (BE): European Union; 2017 [cited 2017 Oct 29]. Available from URL: https://ec.europa.eu/health/sites/health/files/files/documents/2017_02_28_final_study_report_on_off-label_use_.pdf

British National Formulary for Children (BNFC)[13] and the Italian Medicines Agency's (AIFA) list of chemotherapeutic agents and their licensed indications and additional therapeutic uses as supported by peer reviewed literature known as *Farmaci con uso consolidato nel trattamento dei tumori pediatrici per indicazioni anche differenti da quelle previste dal provvedimento di autorizzazione all'immissione in commercio*[14].

Until all medicines for children are appropriately licensed and labelled, the supply of off-label drug information is vital to enhance patient safety (Ventola, 2009). Changes in attitudes towards off-label therapies may be necessary to help prescribers provide the best care possible to their paediatric patients (Hampton, 2007).

1.3 The EU framework for drug development and authorisation

In the European Union (EU), a medicinal product requires a marketing authorisation to be placed on the market (Borg et al, 2014). New applications (post 2005) for certain indications, including cancer, are lodged directly to the European Medicines Agency (EMA), where a technical dossier supporting the products safety, quality and efficacy is assessed by the Committee for Medicinal Products for Human Use (CHMP) during the centralised procedure (Farrell et al, 2006; Casali & Executive Committee of ESMO, 2007). The CHMP's final opinion, which includes the intended use of a product as specified in product labelling, is then sent to the European Commission which grants the centralised marketing authorisation that is valid and binding in all EU Member States and the European Economic Area (EEA) (Shah et al, 2013).

[13]Paediatric Formulary Committee. BNF for Children 2017-2018 [Online]. London (UK): BMJ Group, Pharmaceutical Press, and RCPCH Publications; c2017 [cited 2017 Sep 29]. Available from URL: http://www.pharmpress.com/product/9780857112484/bnfc

[14]Agenzia Italiana del Farmaco. Farmaci off label (Online). Rome (IT): Agenzia Italiana del Farmaco; c2017 [cited 2017 Sep 29]. Available from URL: http://www.aifa.gov.it/content/farmaci-label

1.3.1 The Paediatric Regulation - Regulation (EC) No 1901/2006

In Europe, Regulation (EC) No 1901/2006 (the Paediatric Regulation) established the Paediatric Committee (PDCO) and Paediatric investigation plans (PIPs) to resolve the problem of absence of suitably adapted medicinal products for children. PIPs are binding obligations set by the EMA and its Paediatric Committee, that list the clinical trials and pharmaceutical manufacturing milestones that need to be carried out by a company, specifically in children, during the development of a medicine and before they can submit an application for registration[15] (Zisowsky et al, 2010). Without the result of studies carried out in accordance to the agreed PIP, unless waivered or deferred, a marketing authorisation application for a product intended for use in adults may not pass the validation stage at the start of the licensing procedure (Auby, 2008).

Eleven years have passed since the Paediatric Regulation was published. During this time the Paediatric Regulation has been praised[16] and criticised (McKee & Belcher, 2014; Tomasi, 2014; Rose & Walson, 2015). The discussion of the class waiver system and a possible shift towards a mechanism of action based approached is of interest (Saint-Raymond & Herold, 2012; Vassal et al, 2013; Pearson et al, 2016). A comprehensive report on the state of Paediatric Medicines in the EU has been published[17].

[15] European Medicines Agency. Paediatric medicines: Overview [Online]. London (UK): European Medicines Agency; c1995-2017 [cited 2017 Jan 10]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/about_us/general/general_content_000265.jsp&mid=WC0b01ac0580028e9d

[16] European Medicines Agency. Successes of the Paediatric Regulation after 5 years - EMA/250577/2013 [Online]. London (UK): European Medicines Agency; 2013 [cited 2017 Sep 10]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Other/2013/06/WC500143984.pdf

[17] European Commission. State of Paediatric Medicines in the EU - 10 years of the EU Paediatric Regulation COM (2017) 626 [Online]. Brussels(BE): European Commission; 2017 [cited 2017 Sep 10]. Available from URL: https://ec.europa.eu/health/sites/health/files/files/paediatrics/docs/2017_childrensmedicines_report_en.pdf

1.3.2 Clinical Development Programs (CDPs)

The data required to support the intended use of all new products, such as the clinical indications, posology and route of administration, is generated during a series of clinical trials with distinct endpoints, outcomes and deliverables known as the Clinical Development Program (CDP). The intended use of a product in the context of current therapy modalities influences the type and extent of data required to support its registration. The data supporting a product intended for first-line monotherapy, for example, would be different to body of data required for a product intended for third-line adjuvant treatment. Similarly, the type of cancer, for example whether it is leukaemia or an astrocytoma, may also influence the data required. Companies design different clinical development programs to reflect these differences. The number of patients, type of studies and the duration of studies are important parameters that should be taken into consideration when developing a clinical development program (Umscheid et al, 2011).

The process to obtain a marketing authorisation in the case of oncology medicines is more challenging than that of other medicinal products (Seruga et al, 2015). A well devised strategy for a successful clinical development program increases the likelihood of obtaining a marketing authorisation. Failed products translate in delays in treatment and higher retail costs for products that successfully reach the market[18], which may hinder patient's access to medicines and this is particularly serious in paediatric oncology where about one in four diagnoses lead to death (Kars et al, 2010; Schuhmacher et al, 2016). More innovative drugs reaching the market in a timely

[18] Kermani F, Narayan-Dubois C. Thinking ahead for effective clinical trials [Online]. New York City (NY): Nature research, Macmillan Publishers Limited; c2017[update 2005 Feb 22: cited 2017 Jan 20].Available from URL: http://www.nature.com/bioent/2005/050201/full/bioent844.html

fashion increase the treatment armamentarium within paediatric oncology, which is of benefit to patients.

Acute lymphoblastic leukaemia will be used in this research project to study clinical development of medicines in paediatric oncology in line with aims and objectives. ALL was selected on the basis of the prevalence of the disease, the presence of opportunities and challenges in the area and extensive activity of the pharmaceutical industry in the ALL drug market.

1.4 Acute Lymphoblastic Leukaemia

Leukaemia was established as a medical entity around 1847 and by 1913, four major clinical/cytomorphologic subsets of leukaemia were described (Gaynon et al, 2012). Based on observation of cell morphology and speed of disease onset acute lymphoblastic leukaemia (ALL), acute myeloid lymphoid (AML), chronic lymphocytic leukaemia (CLL), and chronic myeloid leukaemia (CML) were identified (Gaynon et al, 2012).

Lymphoid leukaemia is caused by proliferation of cells belonging to the lymphoid lineage (Ladines-Castro et al, 2016). Acute lymphoblastic leukaemia involves abnormal and rapid proliferation of lymphoid progenitor cells while CLL is a disorder of morphologically mature but immunologically less mature lymphocytes that progressively accumulate in the blood, bone marrow, and lymphatic tissues (Dighiero & Hamblin, 2008; Pui et al, 2008; Terwilliger & Abdul-Hay, 2017). ALL has peak prevalence in children aged 2 and 5 years but also occurs in adults while CLL is

considered to be an adult disease that is extremely rare in children (Institute & National, 2003; Demir et al, 2014)

Proliferation of cells belonging to the granulocytic (neutrophil, eosinophil, basophil), monocytic/macrophage, erythroid, megakaryocytic and mast cell lineages give rise to myeloid leukaemia (Vardiman et al, 2009; Weiskopf et al, 2016).

1.4.1 Evolution of Leukaemia Classification Systems

Several different classifications were proposed to see whether biological differences underlying the heterogeneity of leukemic disease had prognostic implications (Angelescu et al, 2012).

In 1976 the French-American-British (FAB) co-operative group proposed a system of classification for acute leukaemia in attempt to correlate morphological variation of lymphoblasts with prognosis (Bennett et al, 1976; Miller et al, 1981). The FAB classification system for Acute Lymphoblastic leukaemia subdivided lymphoblastic leukemia into three subtypes, L1 to L3 based on morphological assessment (Bennett et al, 1989). The French-American-British L3 acute lymphoblastic leukemia (L3 ALL) described a morphologically distinct subgroup of ALL and was referred to as mature B-cell ALL or Burkitt leukemia (Velangi et al, 2002; Worch et al, 2013). The FAB classification system continued to be updated until 1989 but has since been replaced by the WHO classification system that allows clinicians to take more clinically relevant treatment decisions (Bennett et al, 1989; Chiaretti et al, 2014).

In 1997, the WHO proposed a classification of neoplastic diseases of the hematopoietic and lymphoid tissues where three types of ALL, namely B lymphoblastic, T lymphoblastic and Burkitt-cell leukemia were categorised based on the morphology and immunophenotype of the leukemic blasts (Harris et al, 1999; Chiaretti et al, 2014; Terwilliger & Abdul-Hay, 2017). The WHO Classification of the Hematopoietic and Lymphoid Tissues of 2001 formally incorporated genetic information in diagnostic schemes for haematological malignancies (Vardiman et al, 2002; Vardiman et al, 2009). This same publication acknowledged that future revision would be necessary as genomic science in oncology advanced (Vardiman et al, 2009). In 2008 and 2016 the WHO published revisions to the WHO classification of myeloid neoplasms and acute leukaemia (Campo et al, 2011; Arber et al, 2016).

Based on improved understanding of lymphoblastic leukaemia, the 2008 revision reclassified ALL as B lymphoblastic leukaemia/lymphoma, not otherwise specified (NOS), B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities and T cell acute lymphoblastic leukaemia/lymphoma (T-ALL) (Chiaretti et al, 2014). Following the 2008 WHO revision Burkitt-cell Leukaemia (FAB L3 ALL) was considered to be the same as Burkitt Lymphoma and is now classified under mature aggressive B-cell neoplasms which are diagnostically and prognostically separate from precursor B-ALL (Rimsza et al, 2017; Terwilliger & Abdul-Hay, 2017).

The WHO 2016 classification for Lymphoblastic Leukemia/Lymphoma introduced relatively minor refinements which included some provisional entities to the classification of ALL (Table 1) (Arber et al, 2016)

Table 1-1: WHO classification of acute lymphoblastic leukaemia (Reproduced from Terwilliger T, Abdul-Hay M. Acute lymphoblastic leukemia: a comprehensive review and 2017 update. Blood Cancer J. 2017;7:e577).

B lymphoblastic leukaemia/lymphoma
B lymphoblastic leukaemia/lymphoma, NOS
B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukaemia/lymphoma with t(9;22)(q34.1;q11.2);BCR-ABL1
B lymphoblastic leukaemia/lymphoma with t(v;11q23.3); KMT2A rearranged
B lymphoblastic leukaemia/lymphoma with t(12;21)(p13.2;q22.1); ETV6-RUNX1
B lymphoblastic leukaemia/lymphoma with hyperdiploidy
B lymphoblastic leukaemia/lymphoma with hypodiploidy
B lymphoblastic leukaemia/lymphoma with t(5;14)(q31.1;q32.3) IL3-IGH
B lymphoblastic leukaemia/lymphoma with t(1;19)(q23;p13.3);TCF3-PBX1
Provisional entity: B lymphoblastic leukaemia/lymphoma, BCR-ABL1-like
Provisional entity: B lymphoblastic leukaemia/lymphoma with iAMP21
T lymphoblastic leukaemia/lymphoma
Provisional entity: Early T-cell precursor lymphoblastic leukaemia
Provisional entity: Natural killer (NK) cell lymphoblastic leukaemia/lymphoma

Principles of the WHO classification system forms the basis for current diagnostic practices in ALL which integrate physical examination, medical history, study of cell morphology, immunophenotype and genetic characterisation (Chiaretti et al, 2014). The correct diagnosis must be established to ensure the best outcome possible for the child (Rivera & Ribeiro, 2014). Misdiagnosing a leukaemia as a less aggressive subtype could potentially result in suboptimal or inadequate treatment but at the same time unnecessarily over-treating a less aggressive subtype with high-intensity regimens is potentially harmful because of the risk of significant toxicity (Chessells, 2001).

1.4.2 Establishing Clinical Diagnosis and Classification

Over 50% of children with leukaemia present with nonspecific clinical presentation of fever, malaise and poor appetite (Hunger & Mullighan, 2015; Clarke et al, 2016). Hallmarks of underlying pancytopenia such as mucosal bleeding, bruising and pallor are usually present (Smithson et al, 1980; Roganovic, 2013). A palpable liver and spleen may be observed together with enlarged lymph nodes and in T-lineage ALL, a possible

mediastinal mass (Attarbaschi et al, 2002; Murakami & Shimizu, 2013; Clarke et al, 2016).

Complete blood counts are performed following physical examination and medical history evaluation (Davis et al, 2014; Jacob, 2016). Blood counts abnormalities are observed in children with leukaemia and in other diseases such as aplastic anaemia (Chessells, 2001). In acute leukaemia, pancytopenia that is secondary to bone marrow infiltration by blast cells is normally present (Clarke et al, 2016). At this point the child is referred to haematologist-oncologist for further investigation if leukaemia is suspected.

Peripheral blood smears narrow potential differential diagnosis by confirming the presence of blast cells in circulation and observing morphological changes in haematocytes (Amin et al, 2005; Bain, 2005; Adewoyin & Nwogoh, 2014). Definitive diagnosis of acute lymphoblastic leukaemia follows cytological examination of bone marrow aspirate to confirm presence of 20% or more lymphoblasts in the bone marrow (Riley et al, 2009; Alvarnas et al, 2015; Terwilliger & Abdul-Hay, 2017).

Immunophenotypic analysis using flow cytometry utilises cell surface antigens to further confirm the cell lineage involved, namely if B-cell or T-cell lineage ALL is present (Riley et al, 2002; Bassan & Hoelzer, 2011; Bleahu et al, 2011; Inaba et al, 2013; Chiaretti et al, 2014). Antigens CD19, CD22, and CD79a are strongly expressed in most cases of B-lymphoblastic leukemia/lymphoma as opposed to T-Lymphoblastic Leukemia/Lymphoma that almost always shows moderate to bright expression of CD3 together with other T lineage–associated markers including CD1a, CD2, CD4, CD5,

CD7, and CD8 that are variably expressed (Peters & Ansari, 2011; Peters & Ansari, 2011; Boyd et al, 2013).

Genetic characterisation is performed after the immunophenotype is established to facilitate optimal risk stratification and treatment planning. Recurrent genetic abnormalities associated with B lymphoblastic leukaemia are detected using karyotyping of G-banded metaphase chromosomes (conventional cytogenetics), interphase fluorescence in situ hybridization (FISH) and reverse transcriptase polymerase chain reaction (RT-PCR) testing (Mrózek et al, 2009; Mullighan, 2012; Inaba et al, 2013; Baughn et al, 2015). The detection of the presence of Philadelphia chromosome in children with ALL is rare in childhood ALL (1%–3%) but important since this affects response to therapy and clinical outcome and requires different treatment to Philadelphia negative (Ph-) ALL (Kang et al, 2016).

1.4.3 Treatment of acute lymphoblastic leukaemia

In paediatric oncology, medicinal products are used within the context of protocols which have been mutually agreed to by international specialists and are based on established use. Treatment protocols are detailed plans on the therapeutic methods used to manage a malignancy and within these protocol drugs are used as monotherapy or in combination chemotherapy regimens. The priority of treatment is determined and products or combinations of products, are classified as first-line treatments or as subsequent treatments (Chabner & Roberts, 2005).

Modern leukaemia treatment follows “risk-adapted” therapy principles to the effect that clinical protocols that vary duration, complexity and intensity are used. Other treatment

modalities such as radiation and bone marrow transplantation may also be incorporated into the leukaemia treatment stratagem. ALL risk stratifications systems are based on several factors proven to greatly influence prognosis. Some of these factors include the age of onset, immounophenotypes (e.g B or T cell linage), underlying genetic mutations (e.g oncogenic BCR-ABL gene fusion found Philadelphia positive cancers) and outcome of previous treatment (e.g relapsed or refractory disease status).

All current acute lymphoblastic leukaemia treatment protocols have a multi drug chemotherapy backbone. The treatment of ALL is most often divided into three consecutive phases or blocks termed as induction phase, consolidation phase and maintenance phase (Rudin et al, 2017). The total duration of all phases is between 2 to 3 years (Cooper & Brown, 2015).

The induction phase is the first phase of ALL treatment and lasts between 4 and 6 weeks. The aim of the induction phase of treatment is to induce remission of the disease. Complete remission (CR) is the term used to describe successful induction and has been traditionally defined as restoration of normal haematopoiesis with a blast cell fraction of less than 5% as determined by morphological examination of a bone marrow sample by light microscopy (Pui & Campana, 2000). More recently minimal residual disease (MRD) has been used to describe remission status. MRD describes the presence of disease at the molecular level and better indicates if remission has been achieved. The presence of tumour cells is detected by laboratory techniques such flow cytometry and quantitative polymerase chain reaction that are more sensitive than morphologic examination (Pui & Campana, 2000; Paietta, 2002).

The chemotherapeutic backbone of most induction regimens includes a combination of vincristine, an anthracycline, such as daunorubicin or doxorubicin, corticosteroids such as prednisone or dexamethasone and L-asparaginase (Jabbour et al, 2005; Fullmer et al, 2009; Stock, 2010; Freireich et al, 2014).

The consolidation phase follows the induction phase if CR is achieved. Consolidation involves intensification of treatment to further eliminate residual leukemic cells and involves chemotherapeutic agents not used in the induction phase (Kato & Manabe, 2018). Mercaptopurine, thioguanine, methotrexate, cyclophosphamide, etoposide, and cytarabine are included in the consolidation phase of most ALL treatment protocols (Cooper & Brown, 2015).

The final phase is the Maintenance Phase, where children receive oral chemotherapy on an outpatient basis for about 2 years. The 6-mercaptopurine (6MP) and methotrexate (MTX) combination has been proven to be effective maintenance therapy in ALL (Schmiegelow et al, 2014). Some protocols add monthly vincristine and steroid pulses to the oral 6-mercaptopurine and methotrexate combination to help prevent bone marrow and testicular relapse (Bleyer et al, 1991; Childhood Acute Lymphoblastic Leukaemia Collaborative Group, 2010)

During the leukaemia treatment intrathecal (IT) chemotherapy is given to eliminate the disease that has infiltrated into the cerebrospinal fluid (CSF), a so-called pharmacologic "sanctuary site". In males, overt testicular involvement may occur and must be treated (Hijiya et al, 2005). Other drugs and other supportive measures such a hydration are used during the treatment of ALL. Drugs used for supportive care include, allopurinol to protect the kidneys during tumour lyses syndrome, dexrazoxane a cardiac protector used

during anthracycline based regimens, granulocyte-colony stimulating factors to boost white cell production, leucovorin to counteract methotrexate toxicity and ondansetron to prevent nausea and vomiting (Heath et al, 2003; Skarby et al, 2006; Cohen, 2007; Kremer & van Dalen, 2015; Alakel et al, 2017)

Children with newly diagnosed Ph-positive ALL are treated with tyrosine kinase inhibitors (TKIs) incorporated into the frontline regimens (Leoni & Biondi, 2015). Ph-positive ALL patients historically had poor prognosis when compared to their Ph negative counterparts and were considered to be one of the highest risk paediatric ALL groups (Liu-Dumlao et al, 2012; Yu et al, 2017). In the post imatinib era, patients appropriately treated with intensive chemotherapy and continuous imatinib are estimated to have an overall survival of 70–75% (Schultz et al, 2014)

The intensity of a protocol refers to the number and choice of drugs used as well as the posology (dose/duration) of drugs administered. The intensity and duration of IT chemotherapy is also dependant on such risk stratifications systems. Clinicians strive to use treatment protocols which offer the best chance of cure without unnecessarily exposing the child to unacceptable toxicity.

Children with ALL may relapse both during treatment and after treatment. Relapsed and refractory patients are treated with intensive combination chemotherapy, most often with the same combinations of drugs used in first line treatment and with allogeneic hematopoietic stem cell transplantation (HSCT) (Locatelli et al, 2012). Other agents not typically used in first line regimens such as idarubicin, etoposide, ifosfamide, and mitoxantrone have been studied to improve outcomes of relapsed patient and are considered to be second line agents (Parker et al, 2010; Kelly et al, 2013).

Hematopoietic stem cell transplantation (HSCT) has become an established procedure for haematological diseases including leukaemia and very high-risk ALL patients in first remission or at various stages of relapse have been successfully treated with HSCT (Pulsipher et al, 2011; Henig & Zuckerman, 2014; Cooper & Brown, 2015).

The hematopoietic stem cell source differentiates between the two main types of HSCT used to treat disease (Copelan, 2006; Hatzimichael & Tuthill, 2010). Allogeneic (allo) HSCT involves a stem cell graft from a healthy donor who may be a matched related sibling or a haploidentical (partially matched) family relative although stem cell grafts for allo-HSCT can also be obtained from an unrelated donor (Henig & Zuckerman, 2014). Autologous HSCT uses the patient's own hematopoietic stem cells to restore hematopoietic cell function following the administration of high-dose chemotherapy (Gonçalves et al, 2009).

Allogenic HSCT has been proven to be superior to auto-HSCT for the treatment of ALL (Imamura & Shigematsu, 2015). Recipients receive conditioning treatment prior to the translation procedure. The objective of conditioning treatment is to permit engraftment of healthy donor hematopoietic stem cells, to prevent graft rejection and also to reduce the overall tumour burden (Gyurkocza & Sandmaier, 2014). Conditioning therapy varies in intensity and consists of one of more chemotherapy agents with or without total body irradiation (TBI) (Bevans et al, 2008; Gyurkocza & Sandmaier, 2014). Following conditioning treatment, a haematopoietic allograft harvested from a suitable donor is administered to the recipient intravenously. Engraftment occurs between 10 to 30 days later and patients are monitored closely for lymphocyte recovery and for complications such as infections and graft versus host disease (GVHD) (Kim et al,

2015; Ogonek et al, 2016). The graft-versus leukemia (GVL) effect contributes to the curative nature of HSCT (Dickinson et al, 2017).

1.4.4 Unmet medical needs in Acute Lymphoblastic Leukaemia

Ten-year survival estimates for children newly diagnosed acute lymphoblastic leukaemia have reached 90% however despite this an unmet medical need remains in paediatric ALL (Pui & Evans, 2013; Greaves, 2018).

Current ALL treatment is generally effective but has acute and long-term toxicities. Acute toxicities include opportunistic infections, mucositis, central or peripheral neuropathy, endocrinopathies such as corticosteroid-induced adrenal insufficiency and hyperglycaemia, high-dose methotrexate induced nephrotoxicity, asparaginase-associated hypersensitivity, pancreatitis, and hyperlipidaemia amongst others (Schmiegelow et al, 2017). Long-term effects such as cardiac dysfunction, osteonecrosis, cognitive impairment, and second malignant neoplasms are also of concern (Silverman, 2014). Male survivors of childhood acute lymphoblastic leukaemia are frequently afflicted by infertility, poor semen quality, and gonadal dysfunction (Haavisto et al, 2016).

Toxicity is not the only concern. A percent of paediatric ALL patients are refractory or relapse even after receiving optimum treatment (Bhojwani et al, 2009). Certain genetic and population subgroups subtypes of ALL are at higher risk of relapse and still pose therapeutic challenges (Pui et al, 2011; Pui et al, 2012). One population subgroup associated with poor outcomes is infants with leukaemia and MLL gene rearrangement

where event-free survival in this cohort is estimated between 30% and 40% following intensive therapy (Dreyer et al, 2011; Brown, 2013; Winters & Bernt, 2017).

HSCT is potentially curative but it is associated with acute transplant-related toxicities and mortality (Qazilbash et al, 2009). A significant concern is GVHD which manifests when the transplanted immunocompetent allograft attacks the tissues of the immunocompromised host (Jacobsohn & Vogelsang, 2007). The challenge remains on how to minimise the GVHD while preserving the GVL since these effects are related (Choi & Reddy, 2014). For other patients HSCT is complicated due to a lack of optimal donors (Rocha & Locatelli, 2008)

The unresolved issue associated with current treatment requires that safer and more effective medicines are brought to market to improve treatment of children with ALL.

1.5 Aims and Objectives

The aim of this research was to review the clinical development programs (CDPs) of paediatric oncology medicinal products for acute lymphoblastic leukaemia (ALL) to identify emerging patterns.

The objectives of the study were:

1) To propose prospective treatment protocols for acute lymphoblastic leukaemia based on currently authorised products and drugs in the development phase

2) To examine CDPs of products used to generate the pre-authorisation data as required by regulators

3) To compare the CDPs of products to identify emerging patterns.

Chapter 2
Methodology

2.1 Proposing prospective treatment protocols for Acute Lymphoblastic Leukaemia

Prospective treatment protocols for acute lymphoblastic leukaemia (ALL) were proposed and presented using data elements integral to all clinical treatment protocols, such as antineoplastic drugs used, treatment phase and monitoring parameters used in clinical decision making. Granular details, such as drug doses and the precise day of drug administration were not included in the proposed protocols to avoid overcomplicating the presented treatment protocols.

Different protocols were proposed to reflect the priority of therapy (first line and second line) and the ALL subtype. A protocol for bone marrow transplantation was presented separately. A step-wise approach was used to propose prospective treatment protocols for ALL, with each new step adding data to the protocol representation established. Current treatment protocols for paediatric ALL were retrieved, then EU centrally authorised medicines were incorporated in current treatment protocols. Drugs in the development phase were then integrated into current treatment protocols to form the basis for proposed prospective treatment protocols for ALL. Figure 2-1 outlines the method and sources of data used to create prospective treatment protocols

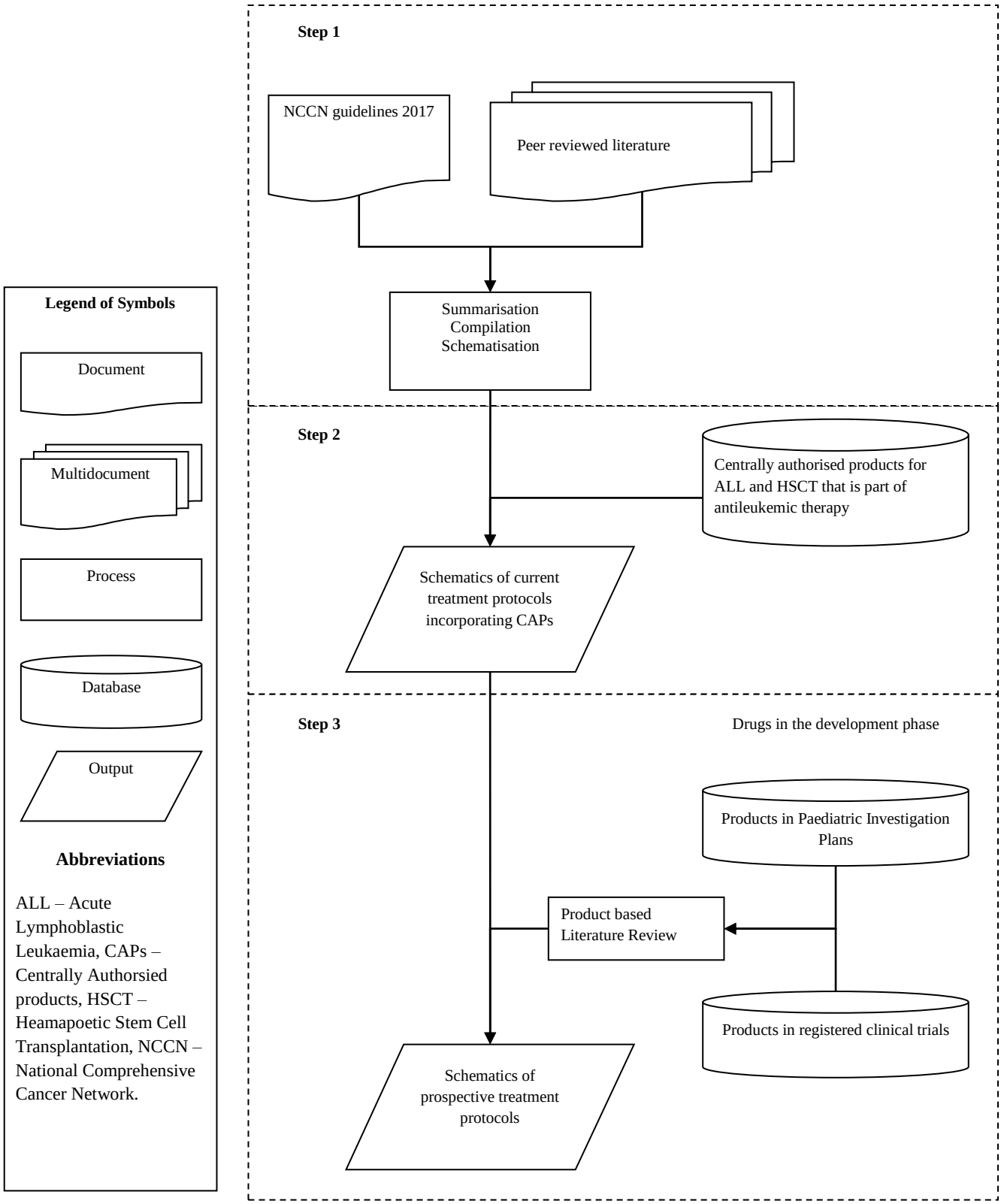

Figure 2-1: Flowchart of method and sources of data used to propose prospective treatment protocols

2.1.1 Current treatment Protocols for ALL

The National Comprehensive Cancer Network (NCCN) guidelines are evidence and consensus based clinical practice guidelines that are published periodically by NCCN and are a recognised standard for clinical policy in oncology (Carlson et al, 2014). NCCN Clinical Practice Guidelines in oncology for Acute Lymphoblastic Leukaemia (Version 4.2017) were obtained from the NCCN website[19]. NCCN guidelines and peer reviewed literature were rationalised to create schematics representing current treatment protocol on which schematics representing prospective treatment protocols were created.

2.1.2 Currently Approved Medicines

Centrally authorised antineoplastic agents were identified from the European Medicines Agency (EMA) online database of European public assessment reports (EPARs)[20]. European public assessment reports are published for every medicinal product that has been granted or refused a marketing authorisation. EPARs are a set of documents which include the product information, namely the package leaflet and summary of product characteristics (SmPC) and the scientific assessment reports for each regulatory application[21].

[19] National Comprehensive Cancer Network. NCCN Guidelines® & Clinical Resources [Online]. Fort Washington (PA): National Comprehensive Cancer Network; c2017 [cited 2017 Sep 12]. Available from URL: https://www.nccn.org/professionals/physician_gls/default.aspx

[20] European Medicines Agency. European public assessment reports [Online]. London (UK): European Medicines Agency; c2017 [cited 2017 May 8]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124

[21] European Medicines Agency. European public assessment reports: background and context [Online]. London (UK): European Medicines Agency; c2017 [cited 2017 May 8]. Available from URL:

EU products were filtered using the Anatomical Therapeutic Chemical (ATC) classification of the World Health Organization (WHO)[22] prior to retrieval. All centrally approved antineoplastic agents (L01) authorised until November 2017 were retrieved. Products which were refused a marketing authorisation were excluded. The SmPCs of all antineoplastic agents (L01) were reviewed to check for a paediatric indication in ALL. Only products licensed with paediatric indications in Acute Lymphoblastic Leukaemia were considered.

Centralised products for hematopoietic stem cell transplantation (HSCT) were also retrieved from the European Medicines Agency online database of European public assessment reports since HSCT is an integral part of antileukemic therapy. Centralised products for HSCT were identified by filtering authorised products by therapeutic area. The SmPCs of all products for HSCT were reviewed. Only products that are part of conditioning regimens or are adjuncts to HSCT and are indicated in children were included in this study. Generic and biosimilar products of centrally approved products (CAPs) were excluded because the marketing authorisation of a generic medicinal product is supported by bioequivalence (BE) studies instead of full clinical trials for safety and efficacy (Refalo et al, 2017).

CAPs with paediatric indication in ALL and HSCT that is part of antileukemic therapy, were integrated into the treatment schematic representing current protocols for treating paediatric ALL, based on the wording of the approved therapeutic indications (section 4.1 of the EU-SmPC). For example, Evoltra (clofarabine) is indicated for "*Treatment of*

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http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/general/general_content_000433.jsp&mid=WC0b01ac058067fa26

[22] WHO Collaborating Centre for Drug Statistics Methodology. ATC/DDD index 2017 [Online]. Oslo (NO): Norwegian Institute of Public Health; c2009 [updated 2016 Dec 19; cited 2017 Jan 11] Available from URL: http://www.whocc.no/atc_ddd_index/

acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response"[23] therefore Evoltra was classified as a third line monotherapy since according to the European Union (EU) SmPC patients must have failed two prior regimens before the product is used.

Jylamvo (methotrexate oral solution) is indicated for: "*Maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over*"[24]. Published literature further confirmed that the oral methotrexate formulations are widely accepted as an integral part of maintenance phase of all treatment regimens of paediatric acute lymphoblastic leukaemia. Based on the indication Jylamvo is a first line agent which is always used in combination with other substances during the maintenance phase of all treatment protocols.

2.1.3 Drugs in the Development Phase

Three online data sources were used to identify drugs in the development phase.

1. The EU Clinical Trials Register[25]
2. EMA database for opinions and decisions on Paediatric Investigation Plans[26]

[23] European Medicines Agency. Product Information for Evoltra - EMEA/H/C/000613 -IB/0057 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2017 Nov 14; cited 2018 Mar 11]. Available from URL: http://www.ema.europa.eu/ema
[24] European Medicines Agency. Product Information for Jylamvo - EMEA/H/C/003756 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 April 19; cited 2018 Mar 15] Available from URL: http://www.ema.europa.eu/ema
[25] European Medicines Agency. EU Clinical Trials Register [Online]. London(UK): European Medicines Agency; c1995-2017 [cited 2017 Nov 11]. Available from URL: https://www.clinicaltrialsregister.eu/ctr-search/search
[26] European Medicines Agency. Opinions and decisions on paediatric investigation plans [Online]. London (UK): European Medicines Agency; c1995-2017 [cited 2017 Jan 11]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/pip_search.jsp&mid=WC0b01ac058001d129

3. US National Library of Medicine database of clinical trials at ClinicalTrials.gov[27]

The EU Clinical Trials Register contains information on interventional clinical trials conducted in the European Union and the European Economic Area (EEA) which started after 1 May 2004. Clinical trials conducted outside the EU/EEA are included in the EU Clinical Trials Register if (i) they form part of a paediatric investigation plan, or (ii) they are sponsored by a marketing authorisation holder and involve the use of a medicine in the paediatric population as part of an EU marketing authorisation[28].

The EMA makes all opinions and decisions on Paediatric Investigation Plans available through a searchable online database. The PDCO allows marketing authorisation (MAHs) to carry out paediatric studies after the activity and safety of the product in adults has been confirmed (Rocchi & Tomasi, 2011). Additional prospective products for which clinical trials in children have been deferred may be identified by reviewing PIPs published by the PDCO.

The online resource ClinicalTrials.gov provides public access to information on publicly and privately supported clinical studies conducted around the world[29].

The use of 3 sources of data provided a comprehensive picture of potential future products currently being developed for children with ALL.

[27] U.S National Library of Medicines. Clinical trials.gov [Online]. Bethesda (MD) National Institutes of Health, c2012 [cited 2017 Nov 11]. Available from URL: https://clinicaltrials.gov/

[28] European Medicines Agency, Heads of Medicines Agencies. About the EU Clinical Trials Register (Online). London (UK): European Medicines Agency; c1995-2017 [cited 2017 Oct 18]. Available from URL: https://www.clinicaltrialsregister.eu/about.html

[29] U.S National Library of Medicines. Background to Clinicaltrials.gov [Online]. Bethesda (MD) National Institutes of Health, c2012 [cited 2017 Nov 11]. Available from URL: https://clinicaltrials.gov/ct2/about-site/background

2.1.3.1 Prospective products described in Paediatric Investigation Plans

Paediatric investigation plans (PIPs) in oncology, including deferrals and waiver were retrieved from the EMA database for opinions and decisions on PIPs until November 2017. Paediatric Committee (PDCO) decisions for products that grant a waiver in all age groups for the listed conditions were excluded. The PDCO decisions for which a full waiver was not granted were reviewed to identify substances indicated for treatment of acute lymphoblastic leukaemia since the published decision describes the paediatric conditions and indications for each agreed PIP (Vassal et al, 2013). PIPs concerning substances indicated as part of conditioning treatment prior to haematopoietic-progenitor-cell transplantation or as adjunctive treatment in haematopoietic stem cell transplantation were also identified. The indication(s) targeted by the PIP and the program of clinical development imposed by the PDCO were captured from the EMA-PDCO decisions.

2.1.3.2 Prospective products described in Clinical trials

The EU Clinical Trials Register was searched to retrieve studies relevant to paediatric ALL. The website's inbuilt search and filter functions were used to retrieve relevant studies. The search term used was 'acute lymphoblastic leukaemia' and results were filtered using six age range criteria; (i) adolescents, (ii) children, (iii) infant and toddler, (iv) newborn, (v) preterm new born infants and (vi) under 18s. All clinical trials fulfilling the search criteria and registered from 1st May 2004 until November 2017 were retrieved. Each study was reviewed for inclusion using 2 inclusion and 6 exclusion criteria (Table 2-1).

Table 2-1: Inclusion and exclusion criteria for selecting clinical trials registered in the EU clinical trial register and the United States national library of medicine database of clinical trials

Inclusion Criteria	Exclusion Criteria
1) Studies investigating prospective novel products (including novel formulations) for ALL or HSCT that is part of antileukemic therapy 2) Studies investigating authorised products that are used in ways outside the authorised indication. These included, for example, studies investigating the efficacy and safety of products currently only indicated for use in adults, in children. Or studies investigating the use of products currently authorised in children for first or second relapse leukaemia, as higher priority agents, either alone or within combination chemotherapy regimens	1) Studies used to support the applications of current CAPs. These studies were reviewed during the analysis of clinical development programs retrieved from EPARs (see section 3.4.1). 2) Studies to optimise the safety and efficacy of chemotherapy regimens based on authorised products by investigating the timing of drugs, duration of drug treatment and dose. 3) Studies to optimise the selection of bone marrow donors and bone marrow transplantation procedures and studies investigating products associated with HSCT that were not part conditioning treatment prior to haematopoietic-progenitor-cell transplantation or as adjunctive treatment in haematopoietic stem cell transplantation. These included, for example, studies investigating the use of immunosuppressants for graft-versus-host disease prophylaxis and studies to optimise the use of granulocyte colony-stimulating factors prior to stem cell harvest from donors. 4) Studies investigating solely conditions falling outside the WHO 2016 definition of ALL. For example, studies investigating products to treat mature B-cell acute lymphoblastic leukaemia and Burkitt's lymphoma or AML. 5) Studies investigation products to mitigate or manage side effect of antitumor treatment or other products to be used in children diagnosed with ALL 6) Other studies deemed not relevant to the research question at hand. For example, studies where the intervention was not a drug.

The search term used to retrieve relevant studies from clinicaltrials.gov was ‘Acute Lymphocytic Leukemia, Pediatric’ and results were filtered using the ‘Child (birth–17)’

age group. All clinical trials fulfilling the search criteria and registered until November 2017 were retrieved. Observational studies were excluded, as were interventional studies where the intervention was a device, a diet, behavioural therapy or an educational program. The remaining studies were reviewed for inclusion with the same inclusion and exclusion criteria that was applied to studies registered in the EU clinical trial register (Table 2-1). If the same study was included both in the EU clinical trial database and clinical trials.gov only information from the EU clinical trial register was used to avoid duplicates.

Following a review of clinical studies, a list of prospective products was compiled and investigational medicinal products (IMPs) were classified as being either of chemical origin, biological or biotechnological origin, or as Advanced Therapy Medicinal Products (ATMPs). ATMPs were further sub classified as somatic cell therapy medicinal products, gene therapy medical product or tissue engineered products.

The data elements captured for each investigational medicinal product were: (i) active substance, (ii) pharmaceutical form, (iii) study aims and (iv) endpoints (both primary and secondary), (v) the patient population (number of patients, inclusion and exclusion criteria), study phase and, where present, the (vi) final outcome. When trials were part of a paediatric investigation plan, additional data from the EU clinical trial register was added to the data retrieved from the PIP decision.

2.1.4 Compiling and Presenting Proposed Prospective Treatment Protocols

Drugs in the development phase were integrated in prospective treatment protocols if trials were in phase 2 or higher and were initiated between November 2007 to

November 2017 to put forward a realistic proposal for prospective ALL treatment protocols for children. The decision to exclude IMPs in phase I and phase I/II trials was based on estimates of likelihood of approval established in literature which was found to be 6.7% for phase I trials of oncology drugs (Hay et al, 2014). The clinical development phase is estimated to take six to seven years on average,[30] based on this information it would be unlikely that products described in trials initiated before November 2007 would reach the market if they have not done so already. IMPs in trials which were halted, withdrawn, terminated and prematurely ended were also excluded in the proposed treatment protocols. Prospective products described in PIPs were incorporated in prospective treatment protocols since the program of paediatric trials agreed in PIPs is mandatory for pharmaceutical companies.

2.1.4.1 Product Review

A literature-based product review was carried out for each forthcoming product identified for inclusion as a prospective treatment. The objective was to better understand the anticipated role that the product being developed could have in prospective treatment protocols. Each product was described in brief to give details on the mode of action and in the case of ATMPs, the manufacturing and administration process involved was also described. The product review also involved the use of other data sources apart from peer reviewed publications such as, pharmaceutical company websites and independent websites, to provide context to the development and commercialisation milestones of the products concerned, where applicable.

[30] PhRMA. Biopharmaceutical Research & Development: The Process Behind New Medicines [Internet]. Pharmaceutical Research and Manufacturers of America; 2015 [cited 2018 mar 15]. Avialable from URL http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf

Following the product-based literature review, drugs in the development phase were incorporated in the proposed treatment schematic protocols developed in this study, according to their anticipated role and priority in treatment based on the data captured from PIPs, the EU clinical trial register and clinicaltrials.gov.

2.2 Review of Clinical Development Programs

The clinical development programs (CDPs) of products indicated for ALL or HSCT that is part of antileukemic therapy were analysed and reviewed. European public assessment reports were used to collect data about the number and nature of studies carried out, in support of the marketing authorisation application. The legal bases for authorisation was noted. The date of authorisation was also noted to allow a comparison of clinical development required to gain market access across time.

IMPs in the development phase were stratified according to phase, and indication area. The EU clinical trial register and clinicaltrials.gov give information about the trial status. The EU clinical trial register uses 4 words to describe the trials status; ongoing, completed, temporarily halted and prematurely ended while clinical trial.gov uses 9 terms to describe the trial status. Five descriptive words were adopted to cater for terms used by both data sources to simplify analysis of trial status, these were; (i) ongoing, (ii) completed, (iii) temporarily halted, (iv) terminated and (v) unknown.

The status temporarily halted refers to trials stopped but which may be resumed. Terminated refers to trials that have been stopped early and will not start again. Unknown is a term exclusively used by clinicaltrials.gov and refers to previously

ongoing trials that have passed their expected completion date however the true status has not been verified within the past 2 years.

PIPs outlining studies for prospective products for paediatric ALL were summarised in table format and the number and nature (e.g dose finding study or open-label, randomised, controlled trial) of clinical trials were considered.

2.3 Comparative analysis to detect emerging patterns

Three sets of CDPs were compared based on phase II trials or higher of different products with the aim of detecting emerging patterns (Table 2.2). Differences in the number of studies, type of studies, number of patients and the primary endpoints used to support the product labelling were presented and examined.

Table 2-2: Summary of CDP comparisons and rationale for selection

Comparison	Rationale for Selection
Authorised and prospective asparaginase depleting agents	Represent efforts by the industry to develop novel formulations of established products
Authorised and prospective tyrosine tinase Inhibitors	Represents efforts by the industry to develop new drugs for paediatric Ph+ ALL within a drug generations framework
Two new prospective products; a biological BiTE monoclonal antibody and a CAR-T cell based ATMP	Represents efforts by the industry to develop new drugs in novel drug categories for relapsed or refractory ALL

Abbreviations: ALL, Acute Lymphoblastic Leukaemia; ATMP, Advanced Therapy Medicinal Product; BiTE, Bispecific T engager; CAR-T cell, Chimeric Antigen Receptor T Cells; Ph+, Philadelphia chromosome positive.

2.4 Publication of Abstract

An abstract entitled “Emerging patterns in the clinical development of medicines in paediatric oncology” was submitted for 78th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences that will be held between the 2nd and 6th September 2018 in Glasgow, UK. The abstract submitted was accepted (FIPSUB-2248) for a poster presentation session (refer to FIP Presentation section).

Chapter 3
Results

3.1 Centrally Authorised Products for Paediatric ALL

One thousand two hundred and five products were granted a central marketing authorisation by the European Commission between October 1995 and November 2017 (Figure 3–1). Out of the 1205 products authorised, 153 products were authorised as antineoplastic agents and 13 products were authorised with an indication for haematopoietic stem cell transplantation. Six antineoplastic agents were refused a marketing authorisation and were excluded prior to summary of product characteristics (SmPC) review. Five generics were excluded, 1 generic for Busilvex and 4 generics for Glivec. Four products were excluded because they were indicated in adults with ALL but not in children. Besponsa, Iclusig and Sprycel were indicated for adult ALL and Zalmoxis that was indicated as adjuvant treatment in adults who have received a haematopoietic stem cell transplant.

A total of 9 products met the inclusion criteria set for the study. None of the products identified were withdrawn from the market at the cut-off date for the analysis (November 2017). Products identified for inclusion were granted initial authorisation between November 2001 and March 2017. When considering the approval date of paediatric acute lymphoblastic leukaemia (ALL) or haematopoietic stem cell transplantation (HSCT) indications, the first paediatric indication was granted in October 2005.

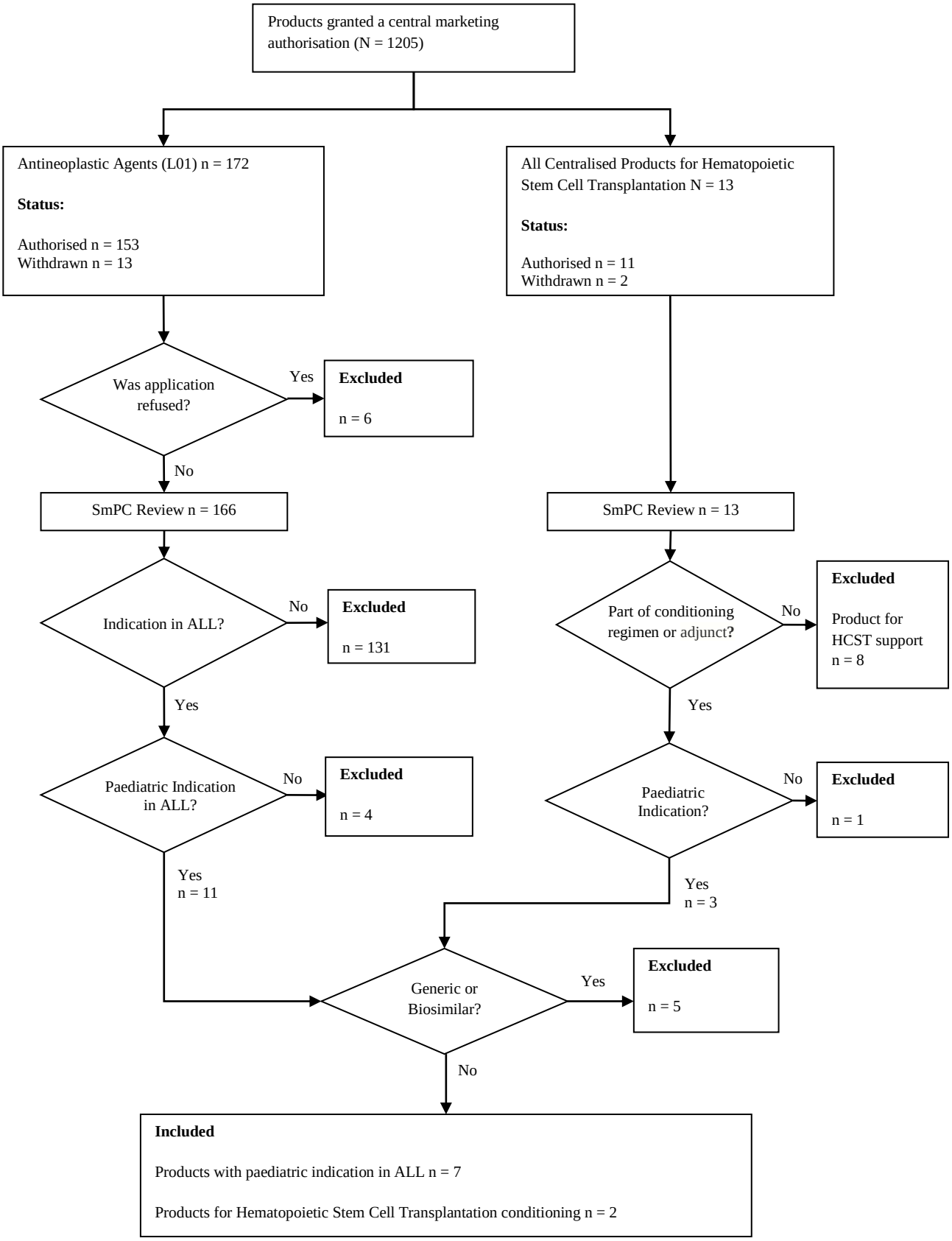


Figure 3-1: Flowchart illustrating the selection of centrally authorised products indicated for the treatment of paediatric ALL and products indicated as conditioning treatment prior to HSCT

Review of therapeutic indications listed in section 4.1 of the EU-SmPC showed that 7 out of 9 products were indicated for ALL and 2 products were indicated as part of conditioning treatment prior to HSCT, in combination with other chemotherapy medicinal products (Table 3-1). Five out of the 7 products for ALL were indicated as part of first line chemotherapy regimens and 2 were indicated as third line monotherapy. The complete indication wording of centrally approved products (CAPs) identified are presented in Annex 1. Seven out of the 9 products were categorised as small molecule and 2 products were categorised as biologicals.

Table 3-1: Overview of CAPs indicated for the treatment of paediatric ALL and products indicated as conditioning treatment prior to HSCT

Medicine Name (Active Substance)	Date of approval of paediatric ALL/HSCT indication	Treatment Priority (Area)	Drug Category
Atriance (Nelarabine)	22/08/2007	Third Line (T-ALL)	Small Molecule
Busilvex (Busulfan)	27/10/2005	Conditioning treatment prior to HSCT	Small Molecule
Evoltra (Clofarabine)	29/05/2006	Third Line (ALL)	Small Molecule
Glivec (Imatinib)	27/06/2013	First Line (Ph+ ALL)	Small Molecule
Jylamvo (Methotrexate)	29/03/2017	First Line (ALL)	Small Molecule
Oncaspar (Pegaspargase)	14/01/2016	First Line (ALL)	Biological
Spectrila (Asparaginase)	14/01/2016	First Line (ALL)	Biological
Tepadina (Thiotepa)	15/03/2010	Conditioning treatment prior to HSCT	Small Molecule
Xaluprine (6-mercaptopurine monohydrate)	15/03/2010	First Line (ALL)	Small Molecule

Analysis of the route of administration showed that 6 out of 9 products were formulated for intravenous use and 3 products were for oral use. The pharmaceutical dosage forms

of the shortlisted CAPs indicated for the treatment of paediatric ALL or products indicated as conditioning treatment prior to HSCT are listed in Table 3–2.

Glivec was the only product with a choice of pharmaceutical form not suitable to all paediatric age groups however Glivec tablets are licensed to be dispersed in a glass of still water or apple juice for patients unable to swallow tablets [31]

Table 3-2: Overview of routes of administration and pharmaceutical form of CAPs indicated for the treatment of paediatric ALL or as conditioning treatment prior to HSCT

Medicine Name (Active Substance)	Route of administration	Pharmaceutical Form(s)
Atriance (Nelarabine)	Intravenous Use	Solution for infusion
Busilvex (Busulfan)	Intravenous Use	Concentrate for solution for infusion
Evoltra (Clofarabine)	Intravenous Use	Concentrate for solution for infusion
Glivec (Imatinib)	Oral Use	Hard Capsule
		Film-coated tablet
Jylamvo (Methotrexate)	Oral Use	Oral solution
Oncaspar (Pegaspargase)	Intravenous Use	Solution for injection/infusion.
Spectrila (Asparaginase)	Intravenous Use	Powder for concentrate for solution for infusion.
Tepadina (Thiotepa)	Intravenous Use	Powder for concentrate for solution for infusion
Xaluprine (6-mercaptopurine monohydrate)	Oral Use	Oral suspension

[31] European medicines Agency. Product Information for Glivec -EMEA/H/C/000406 -II/0108 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 Sep 14; cited 2018 Mar 11]. Available from URL: http://www.ema.europa.eu/ema

3.2 Drugs in the development phase

Drugs in the development phase were identified from opinions and decisions on paediatric investigation plans (PIPs) adopted by the Paediatric Committee (PDCO) and from clinical trials registered in the European Union (EU) Clinical Trials Register and the United States (US) National Library of medicine clinical trial database.

3.2.1 Number of PIPs

One thousand five hundred and ninety-two opinions and decisions on PIPs were adopted by the PDCO between December 2007 and November 2017 (Figure 3-2). Five hundred and twenty-four decisions granted a waiver in all age groups and were excluded. One thousand and sixty-seven PIPs were reviewed to check for an indication in ALL or indication as conditioning treatment prior to HSCT. One thousand and fifty-one PIPs were excluded because the prospective indication was not inclusive of ALL or conditioning/adjunctive treatment prior to haematopoietic stem cell transplantation

Three PIPs were excluded because they referred to products that were already granted a paediatric indication. These were imatinib mesilate (Novartis Europharm Limited; EMEA-000463-PIP01-08-M03), recombinant L-asparaginase (Medac GmbH; EMEA-000013-PIP01-07-M03), and mercaptopurine monohydrate (Nova Laboratories Limited; EMEA-000350-PIP01-08) which corresponded to CAPs Glivec, Spectrila and Xaluprine respectively.

A total of 13 prospective products outlined in PIPs were identified for this study. Nine prospective products were indicated for the treatment of paediatric ALL (Table 3-3) and 4 prospective products were indicated for conditioning/adjunctive treatment prior to haematopoietic stem cell transplantation (Table 3-4).

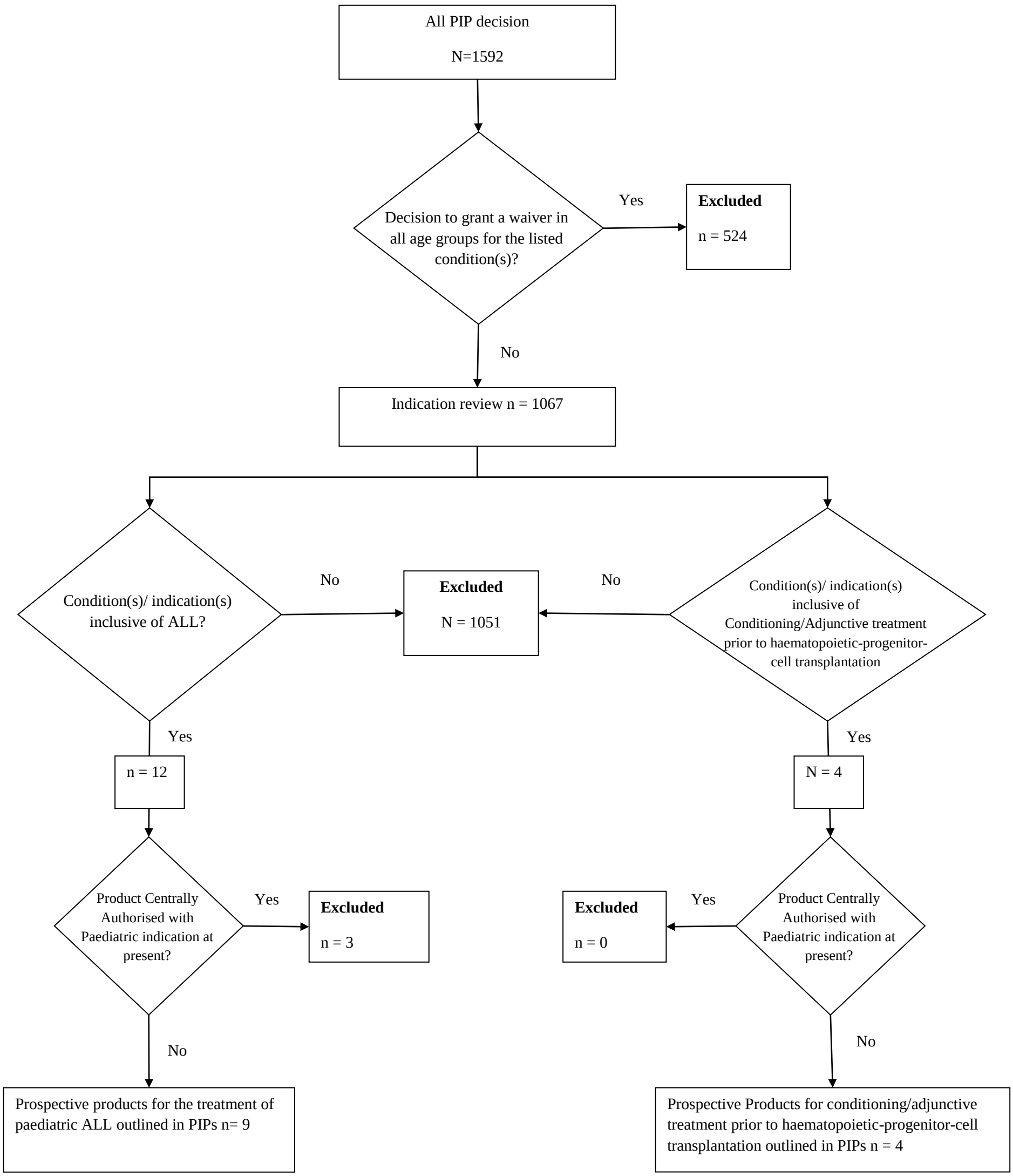


Figure 3-2: Flowchart identifying prospective products for the treatment of paediatric ALL and prospective products for conditioning or adjunctive treatment prior to haematopoietic-progenitor-cell transplantation from the EMA-PDCO opinions and decisions on PIPs

Analysis of drug categories of products described in PIPs for ALL showed that 5 out of 9 products were small molecule, 2 were biologicals and 2 gene therapy medicinal products. With regards to treatment priority, 4 out of 9 products described in PIPs for ALL were proposed as second line treatment, 3 products were proposed as first line treatment and one product (dasatinib) was proposed for both first and second line treatment of Philadelphia chromosome positive (Ph+) ALL (Table 3-3)

Table 3-3: Overview of prospective products for the treatment of paediatric ALL described in PIPs

Active Substance	Decision date (Date of completion)	Proposed Treatment Priority (ALL subtype)	Drug Category
Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 (CTL019)	22/09/2017 (December 2021)	Second Line (B-ALL)	Gene therapy medical product
Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor	09/08/2017 (December 2020)	Second Line (B-ALL)	Gene therapy medical product
Navitoclax (ABT-263)	10/06/2011 (December 2019)	Second Line (ALL)	Small Molecule
Blinatumomab	29/01/2016 (July 2023)	Second Line (B-ALL)	Biological
Cyclophosphamide	27/01/2012 (March 2015)	First line (ALL)	Small Molecule
Dasatinib	02/05/2013 (June 2018)	First Line (Ph+ ALL) Second Line (Ph+ ALL)	Small molecule
L-asparaginase encapsulated in erythrocytes	04/09/2017 (December 2020)	First line (ALL)	Biological
Momelotinib	10/07/2015 (July 2017)	First line (ALL with a Janus kinase (JAK)-activating mutation	Small Molecule
Ponatinib	05/05/2017 (December 2020)	Second line (Ph+ ALL)	Small Molecule

Analysis of drug categories of products described in PIPs for adjuvant or conditioning treatment prior to HSCT showed that 3 out of 4 products were advance therapy medicinal products (ATMPs) of which 2 were gene therapy medicinal products and 1 was a somatic cell therapy medicinal product, and 1 product was a small molecule (Table 3-4).

Table 3-4: Overview of prospective products for conditioning or adjuvant treatment prior to HSCT described in PIPs

Active Substance	Decision date (Date of completion)	Area	Drug Category
Expanded donor-derived allogenic T cells transduced with the retroviral vector expressing the transgenes for inducible caspase9 and the truncated CD19 selectable marker (BPX-501)	24/07/2017 (April 2018)	Adjuvant treatment to HSCT	Gene therapy medical product
Herpes simplex 1 virus thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes	16/04/2014 (December 2022)	Adjuvant treatment to HSCT	Gene therapy medical product
T-lymphocytes enriched leukocyte preparation depleted ex vivo of host host-alloreactive T cells using photodynamic treatment (ATIR101)	21/04/2017 (December 2021)	Adjuvant treatment to HSCT	Somatic cell therapy medicinal product
Treosulfan	02/10/2017 (December 2019)	Conditioning treatment prior to HSCT	Small Molecule

Analysis of routes of administration for products described in PIPs showed that 8 out of 13 products were for intravenous use and 5 were for oral use. All ATMPs and biologicals were for intravenous use and 5 out of the 6 small molecules were for oral administration except for treosulfan which was for intravenous use (Appendix 2).

The average time allowed by the PDCO to complete a PIP for products for ALL and HSCT was 53 months, the median was 47 months. The shortest period was 9 months while the longest was 104 months (Table 3-5).

Table 3-5: Time allowed to complete a PIP in ALL and HSCT by the PDCO

Active Substance	Decision date	Date of completion	Time to complete PIP	
			Months	Year
Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 (CTL019)	September 2017	December 2021	51	4.3
Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor	April 2017	December 2021	56	4.7
Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor	August 2017	December 2020	40	3.3
Blinatumomab	January 2016	July 2023	90	7.5
Cyclophosphamide	January 2012	March 2015	38	3.2
Dasatinib	May 2013	June 2018	61	5.1
Expanded donor-derived allogenic T cells transduced with the retroviral vector expressing the transgenes for inducible caspase9 and the truncated CD19 selectable marker (BPX-501)	July 2017	April 2018	9	0.8
Herpes simplex 1 virus thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes	April 2014	December 2022	104	8.7
L-asparaginase encapsulated in erythrocytes	September 2017	December 2020	39	3.3
Momelotinib	July 2015	July 2017	24	2.0
Navitoclax (ABT-263)	June 2011	December 2019	102	8.5
Ponatinib	May 2017	December 2020	43	3.6
Treosulfan	October 2017	December 2019	26	2.2
		Average	53	4.4
		Median	47	3.9

3.2.2 Products in Clinical Trials

One hundred and twenty trials were retrieved from the EU clinical trial register and 479 trials were retrieved from the US National Library of medicine clinical trial database.

Ninety-six trials were excluded from the dataset retrieved from clinicaltrials.gov prior to review; 75 were observational studies, 10 were trials investigating behavioural therapy and in 11 trials the intervention was a device, a dietary supplement, or an educational program.

In total, five hundred and three trials retrieved from the EU clinical trial register and clinicaltrials.gov were reviewed according to inclusion and exclusion criteria specified (Table 2-1) and 227 trials were included for analysis while 276 trials were excluded from the study. Figure 3–3 outlines the inclusion and exclusion process used. A list of all trials excluded from the study is presented in Appendix 3.

Out of the 227 trials included in this study, 149 trials investigated products for ALL and 78 trials investigated products for conditioning for HSCT or as adjuvant treatment. The number of trials initiated over time for ALL and HSCT is presented in Table 3-6 and Figure 3-4. The number of trials investigating products to treat ALL per year increased over time, reaching an average of 11 trials per year over the 2013 – 2017 period when compared to an average of 2.8 trials per year over the 1995 - 1999 period. The number of trials investigating products for conditioning/adjuvant treatment for HSCT peaked during the 2000 - 2006 period at an average 4.9 trials per year, then maintained at 4.2 trials per year during 2007 – 2012 before declining to an average of 2.4 trials per year over the 2013 – 2017 period.

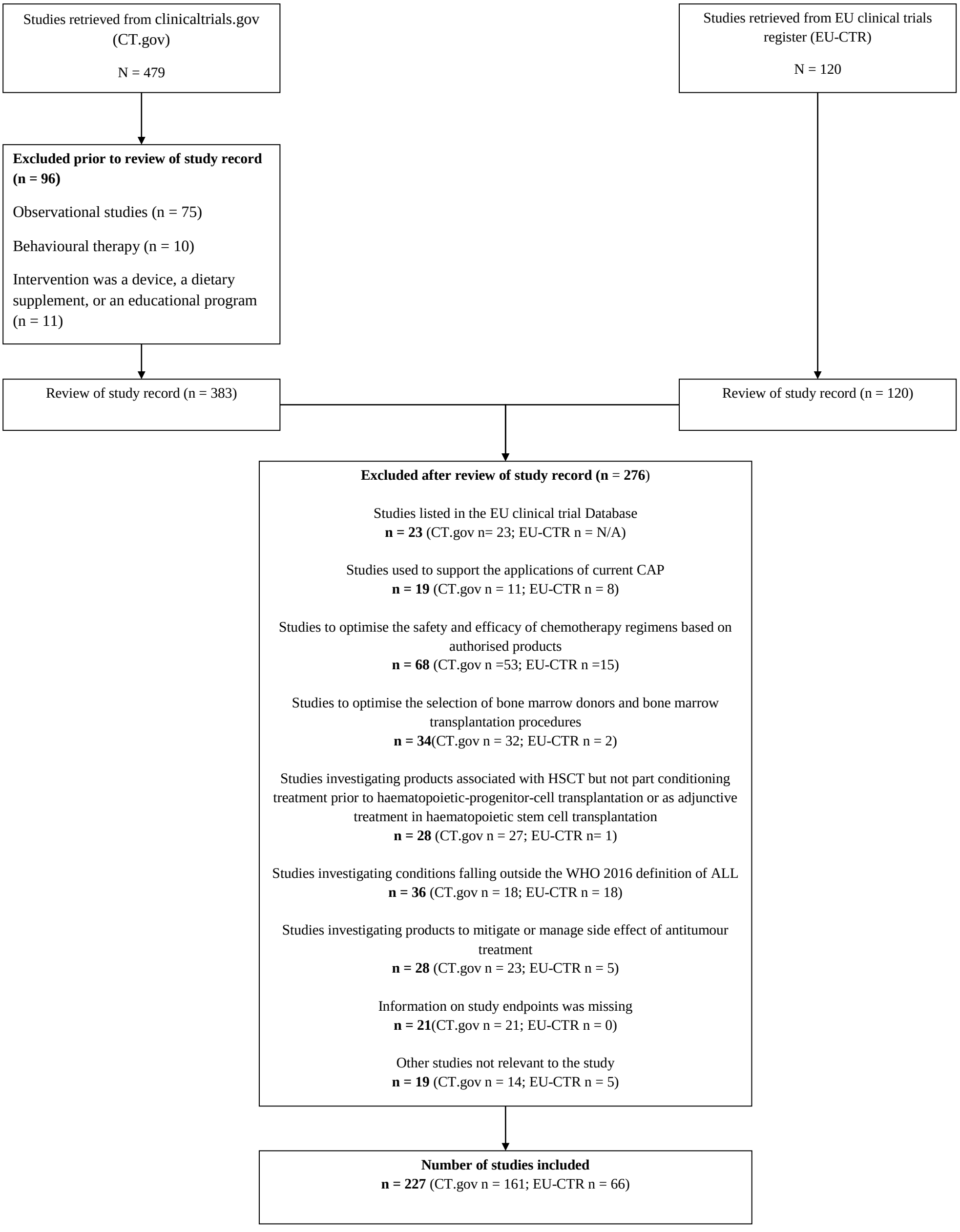


Figure 3-3: Flowchart for identifying prospective products for the treatment of paediatric ALL and HSCT from clinical trials.gov and the EU clinical trial register

Table 3-6: Number of trials initiated over time for ALL and HSCT

Area	**Trials investigating product to treat ALL**			
Years	**1995 - 1999**	**2000 - 2006**	**2007 - 2012**	**2013 - 2017**
Total Trials	11	32	51	55
Average Number of trials / Year	2.8	4.6	8.5	11
Area	**Trials investigating products for conditioning/adjuvant treatment for HSCT**			
Years	**1995 - 1999**	**2000 - 2006**	**2007-2012**	**2013 - 2017**
Total Trials	7	34	25	12
Average Number of trials / Year	1.4	4.9	4.2	2.4

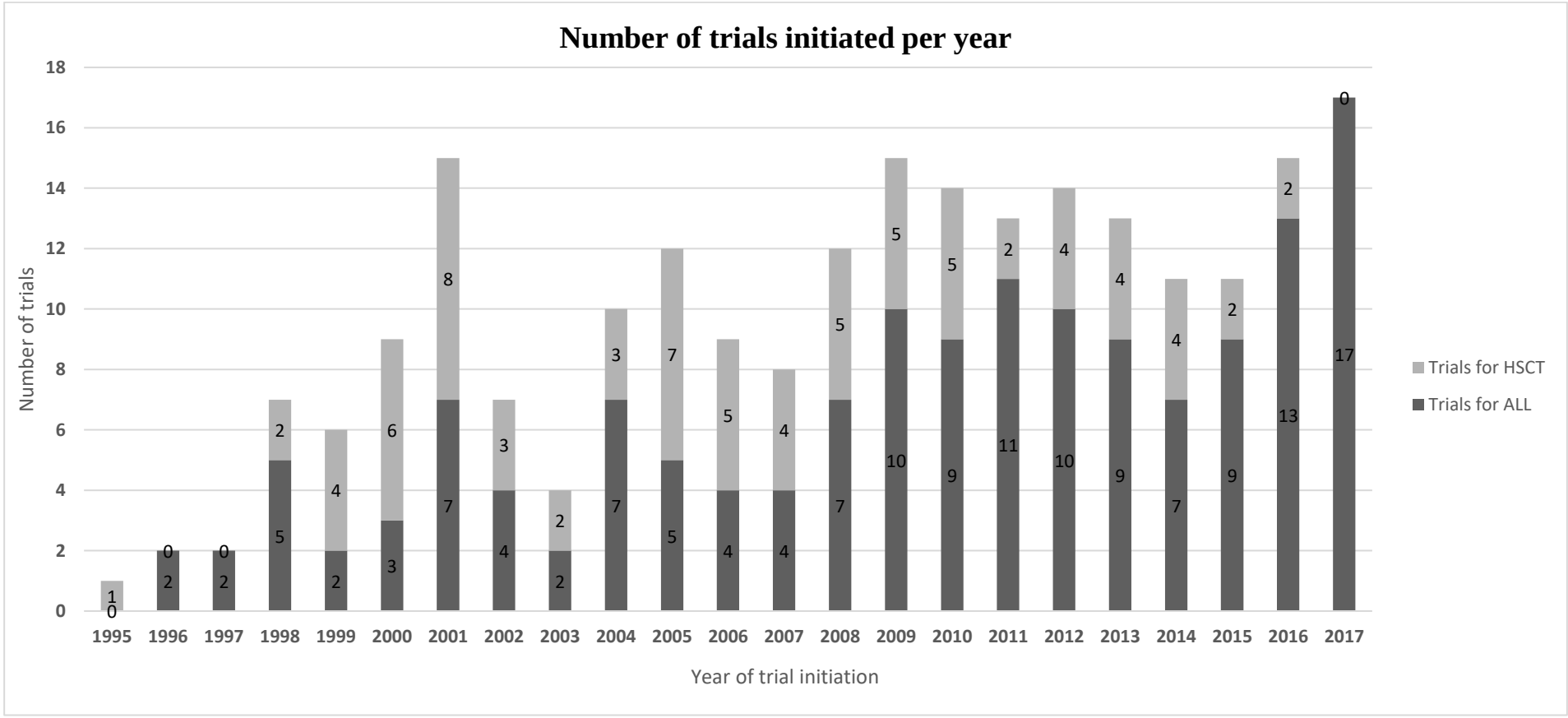


Figure 3-4: Number of trials initiated over time in years categorised per area

3.2.2.1 Clinical trial status and phase analysis

Forty-eight percent of the 227 trials were in the early development phase, that is phase I, phase I/II, and bioequivalence trials (Table 3-7). Phase II trials represented 36% of the trials included in this study while trials in phase II/III, phase III and phase IV collectively comprised 11% of the trials. The clinical trial phase of 5% of the studies was not provided.

Forty-seven percent of 227 trials included in this study were ongoing, while 38% of trials were completed (Table 3-8). Eleven percent of trials were terminated and 4.4% of trials were either temporarily halted or were trials of unknown status. It was observed that 46% of clinical trials investigating products for ALL and 49% of clinical trials investigating products for HSCT were ongoing. Thirty six percent of clinical trials investigating products for ALL and 41% of clinical trials investigating products for HSCT were completed. It was observed that the clinical trials investigating products for ALL had a termination rate of 13% and trials investigating products for HSCT had a termination rate of 6%.

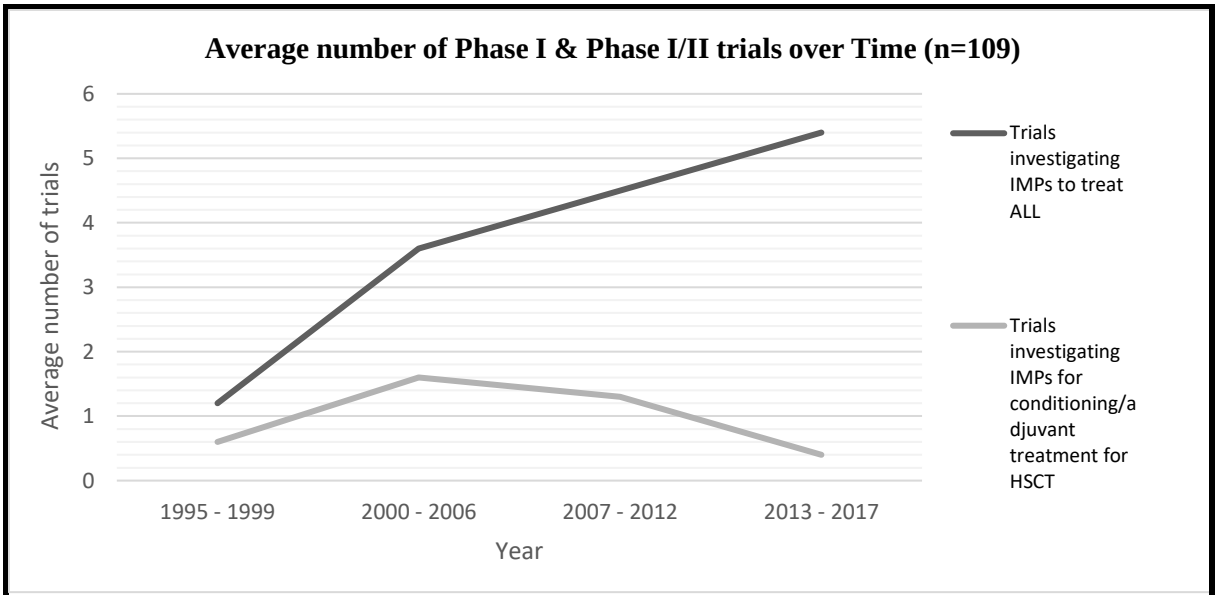
Table 3-7: Number of trials per phase categorised by trial status (N=227)

Phase	**Number of studies *(%)***	**Trial Status**				
		Ongoing	Completed	Temporarily halted	Terminated	Unknown
Not Provided	12 *(5%)*	6	3	-	2	1
Bioequivalence study (BE)	1 *(0.4%)*	-	1	-	-	-
Phase I	78 *(34%)*	22	40	1	13	2
Phase I/II	30 *(13%)*	14	13	1	2	-
Phase II	81 *(36%)*	46	26	-	8	1
Phase II/III	4 *(2%)*	3	1	-	-	-
Phase III	18 *(8%)*	13	2	3	-	-
Phase IV	3 *(1%)*	2	-	-	-	1
Total	227 (100%)	106 (47%)	86 (38%)	5 (2%)	25 (11%)	5 (2%)

Table 3-8: Number of trials initiated over time categorised by trial status (n=227)

Year	Trials investigating products for ALL		Trials investigating products for HSCT		Year Total
	Number of trials	Number of trial per Status	Number of trials	Number of trial per Status	
1995	0	N/A	1	1 Completed	1
1996	2	2 Completed	0	N/A	2
1997	2	2 Completed	0	N/A	2
1998	5	4 Completed, 1 Terminated	2	1 Ongoing. 1 Unknown	7
1999	2	2 Completed	4	3 Completed, 1 Ongoing	6
2000	3	2 Completed. 1 Unknown	6	3 Completed, 3 Ongoing	9
2001	7	6 Completed, 1 Terminated	8	4 Completed, 4 Ongoing	15
2002	4	3 Completed, 1 Terminated	3	2 Completed, 1 Ongoing	7
2003	2	1 Completed, 1 Terminated	2	2 Terminated	4
2004	7	5 Completed, 1 Temporarily Halted, 1 Terminated	3	2 Completed, 1 Ongoing	10
2005	5	3 Completed, 1 Ongoing, 1 Terminated	7	3 Completed, 2 Ongoing, 2 Unknown	12
2006	4	2 Completed, 1 Ongoing, 1 Terminated	5	2 Ongoing, 2 Terminated 1 Completed	9
2007	4	2 Completed, 1 Ongoing 1 Terminated	4	3 Completed, 1 Terminated	8
2008	7	3 Completed, 3 Ongoing, 1 Terminated	5	3 Completed, 2 Ongoing	12
2009	10	4 Ongoing, 4 Terminated, 2 Completed	5	3 Ongoing, 2 Completed	15
2010	9	5 Ongoing, 2 Completed, 2 Terminated	5	3 Ongoing, 2 Completed	14
2011	11	8 Completed, 2 Ongoing, 1 Terminated	2	1 Completed, 1 Ongoing	13
2012	10	6 Ongoing, 2 Terminated, 1 Temporality halted, 1 Unknown	4	2 Completed, 2 Ongoing	14
2013	9	5 Ongoing, 3 Completed, 1 Terminated	4	4 Ongoing	13
2014	7	3 Ongoing, 3 Temporality halted, 1 Completed	4	4 Ongoing	11
2015	9	8 Ongoing, 1 Completed	2	2 Ongoing	11
2016	13	12 Ongoing, 1 Terminated	2	2 Ongoing	15
2017	17	17 Ongoing	0	N/A	17
Totals	**149**	**68 (46%) Ongoing** **54 (36%) Completed** **20 (13%) Terminated** **5 (3%) Temporality halted** **2 (1%) Unknown**	**78**	**38 (49%) Ongoing** **32 (41%) Completed** **5 (6%) Terminated** **3 (4%) Unknown**	**227**

One hundred and nine trials out of the 227 trials analysed were in phase 1, phase I/II or were bioequivalence (BE) trials. Out of 109 phase I and phase I/II trials, 85 trials investigated products for ALL and 24 trials investigated products for HSCT. The average number of phase I and phase I/II trials initiated for products investigated for ALL increased over time while trials initiated for products investigated for HSCT peaked during the 2000 to 2006 period (Figure 3-5).

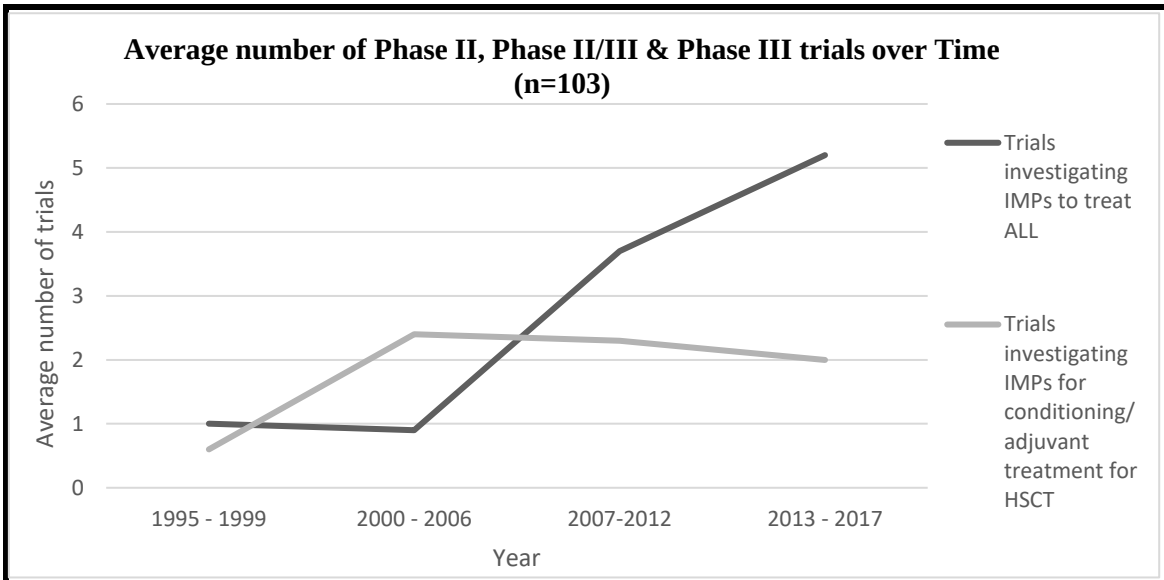


Area	Trials investigating product to treat ALL				Total
Years	**1995 - 1999**	**2000 - 2006**	**2007 – 2012**	**2013 – 2017**	**1995 – 2017**
Total Trials	6	25	27	27	85
Average Number of trials / Year	1.2	3.6	4.5	5.4	3.7
Completed trials	6	16	12	4	38

Area	Trials investigating products for conditioning/adjuvant treatment for HSCT				Total
Years	**1995 - 1999**	**2000 - 2006**	**2007-2012**	**2013 – 2017**	**1995 - 2017**
Total Trials	3	11	8	2	24
Average Number of trials / Year	0.6	1.6	1.3	0.4	1
Completed trials	3	7	6	0	16

Figure 3-5: Number of phase I & phase I/II trials per year from 1995 till 2017.

One hundred and three trials out of 227 trials included for analysis were in phase II, phase II/III and phase III. Out of the 103 trials, 59 investigated products for ALL and 44 trials investigated products for HSCT. The average number of phase II, phase II/III and phase III trials initiated for products investigated for ALL increased over time while trials initiated for products investigated for HSCT peaked during the 2000 to 2006 period (Figure 3-6).



Area	Trials investigating product to treat ALL				Total
Years	**1995 - 1999**	**2000 - 2006**	**2007 - 2012**	**2013 - 2017**	**1995 – 2017**
Total Trials	5	6	22	26	59
Average Number of trials / Year	1	0.9	3.7	5.2	2.6
Proportion of completed trials	4	5	5	1	15

Area	Trials investigating products for conditioning/adjuvant treatment for HSCT				Total
Years	**1995 - 1999**	**2000 - 2006**	**2007-2012**	**2013 - 2017**	**1995 – 2017**
Total Trials	3	17	14	10	44
Average Number of trials / Year	0.6	2.4	2.3	2	1.9
Proportion of completed trials	1	7	5	0	13

Figure 3-6: Number of phase II, phase II/III & phase III trials per year from 1995 till 2017.

3.2.2.2 Drug categories analysis

Drug category analysis of phase I, phase I/II and BE trials showed 74 out of 109 trials investigated small molecules, 21 trials investigated ATMPs, 7 trials investigated biologicals, and 6 trials investigated antibody conjugates (2 antibody-drug conjugates (ADCs), 3 immunotoxins, 1 antibody radionuclide conjugate). One trial (NCT00343798) investigated a small molecule and an ATMP simultaneously.

Drug category analysis of phase II, phase II/III & phase III showed 68 out of 103 trials investigated small molecules, 18 trials investigated ATMPs, 11 trials investigated biologicals, 4 trials investigated antibody conjugates (2 antibody-drug conjugates, 1 immunotoxin and 1 antibody radionuclide conjugate) and 2 trials investigated chemicals and biologicals simultaneously.

3.2.2.3 Patient recruitment analysis

Prior to analysis of the number of patients recruited in 109 phase I, phase I/II and BE trials, 5 additional trials were excluded because of low accrual or due to lack of recruitment information. Trials NCT00458744, NCT00957320, NCT00555048 and NCT00643240, were excluded because they enrolled between 0 and 1 patient and their trial status was described as terminated. One trial, NCT00027547 lacked enrolment information in the study record and was excluded. Patient recruitment analysis for phase I, phase I/II and BE trials per area and drug category is presented in Table 3–9 and patient recruitment analysis for phase I, phase I/II and BE trials over time is presented in Table 3–10. For the 104 phase I, phase I/II and BE trials analysed, the average

number of patients enrolled was 41 patients, the median was 30, and range varied from 3 patients to 302 patients.

Table 3-9: Patient recruitment in phase I, phase I/II and bioequivalence trials per area and drug category

	Area		Drug Category			
	Trail for HSCT	Trials for ALL	Small molecules	ATMPs	Biologicals	ADC & immunotoxins
Average number of patients recruited	41	41	37	40	108	55
Median number of patients recruited	24	30	28	37	89	40
Range of patients recruited	5 – 148	3 - 102	3 - 148	15 - 120	4 - 302	15 - 98
Number of trials analysed	22	82	71	21	7	5

Table 3-10: Average patient recruitment in phase I, phase I/II and bioequivalence trials over time

	Years			
	1995 - 1999	**2000 - 2006**	**2007 - 2012**	**2013 - 2017**
Average number of patients recruited	14	51	33	45
Median number of patients recruited	7	37	23	30
Range of patients recruited	3-31	4 – 302	4 - 129	8 - 148
Number of trials analysed	9	35	31	29

When considering the age groups of recruited patients in 109 phase I, phase I/II trials and BE trials, 12% of trials enrolled exclusively children under 18, while 31% of trials enrolled children and young adults up to 21 years old, the rest (57%) recruited both children and adults. The greatest proportion of trials investigated different haematological malignancies (35%), followed by ALL (26%) and leukaemia (25%). Only 15% of phase I, phase I/II trials and BE trials investigated mixed disease of solid and haematological malignancies.

Prior to analysis of the number of patients recruited in the 103 phase II, phase II/III and phase III trials included in this study, 2 additional trials were excluded because of low accrual. Trials NCT00941928 and NCT00450983 enrolled 2 patients or less and their trial status was described as terminated. Patient recruitment analysis in phase II, phase II/III and phase III trials per area and drug category is presented in Table 3-11 and patient recruitment analysis in phase II, phase II/III and phase III trials over time is presented in Table 3-12. The average number of patients enrolled in 83 phase II and phase II/III trials, was 83, the median was 56, and the range varied from 3 to 1000 patients. The average number of patients enrolled in the 18 phase III trials was 1098, the median was 475 and the range varied from 55 to 5437 patients.

Table 3-11: Patient recruitment in phase II, phase II/III and phase III trials per area and drug category

Phase II and Phase II/III						
	Area		Drug Category			
	Trial for HSCT	Trials for ALL	Small molecules	ATMPs	Biologicals	ADC & immunotoxins
Average number of patients recruited	77	88	74	36	75	58
Median number of patients recruited	54	58	60	27	53	58
Range of patients recruited	12-362	3-1000	3 – 260	10-86	25-240	40-76
Number of trials analysed	41	42	57	12	8	4
Total number of trials analysed	83		81*			

Phase III					
	Area		Drug Category		
	Trial for HSCT	Trials for ALL	Small molecules	ATMPs	Biologicals
Average number of patients recruited	348	1312	1678	417	547
Median number of patients recruited	146	605	830	400	320
Range of patients recruited	100-1000	55- 5437	195-5437	55-1000	82-1242
Number of trials analysed	4	14	10	5	3
Total number of trials analysed	18		18		

**NCT00003816 (362 patients) & NCT03117751 (1000 patients) investigated small molecules and biologicals simultaneously and were excluded from category sub-analysis*

Table 3-12: Average patient recruitment in phase II, phase II/III and phase III trials over time

Phase II and Phase II/III				
	Years			
	1995 - 1999	**2000 - 2006**	**2007 - 2012**	**2013 - 2017**
Average number of patients recruited	93	71	81	91
Median number of patients recruited	46	50.5	66.5	56
Range of patients recruited	11-362	3-260	10-250	10-1000
Number of trials analysed	8	22	26	27
Total number of trials analysed	83			
Phase III				
	Years			
	1995 - 1999	**2000 - 2006**	**2007 - 2012**	**2013 - 2017**
Average number of patients recruited	Not Applicable *No phase III trials were initiated between 1995 and 2006*		1087	1109
Median number of patients recruited			242	550
Range of patients recruited			80-5437	55-4895
Number of trials analysed			9	9
Total number of trials analysed	18			

When considering the age groups of patients recruited in 85 phase II and phase II/III, the greatest proportion of trials (n = 56) recruited both adults and children, 16 trials enrolled exclusively children under 18 years and 13 trials recruited children and young adults up to 21 years old. Thirty-two trials investigated haematological malignancies, 26 trials investigated ALL only, 23 trials investigated leukaemia and 4 trials investigated mixed disease of solid and haematological malignancies.

Eleven trials out of 18 phase III trials recruited both children and adults while 6 enrolled exclusively children (under 18), including one trial (NCT00557193) that recruited infants only. The remaining trial recruited children and adults up to 21 years old. When considering the medical conditions investigated, the greatest proportion of trials (n = 15) investigated only ALL, with the rest (n=3) investigated haematological malignancies. The phase III trials investigating various haematological malignancies rather than ALL only were trials studying products for HSCT.

3.2.2.4 Endpoints Analysis

The choice and number of endpoints was analysed separately for (i) phase I and BE trials, (ii) phase I/II trials, (iii) phase II and phase II/III, and (iv) phase III trials. Endpoints used in phase II and phase II/III trials investigating product for ALL and HSCT were also analysed separately.

Seventy-seven phase I and one BE studies were analysed for choice of primary endpoints and number of endpoints studied. Trial NCT00100152 was excluded for the phase I endpoint analysis because there was no information endpoint in the study record. The number of primary endpoints studied in the 77 phase I trials analysed varied from a single endpoint up to 6 endpoints. The average number of endpoints investigated

in phase I trials was 3.1 and the mode was 3 endpoints. The most frequent endpoint was maximum tolerated dose (MTD) which was observed in 43 out of 78 trials. The second most frequent endpoint was dose limiting toxicity (DLT) which was observed in 28 trials.

Efficacy related endpoints such as measures of response rate like complete remission (CR), partial remission (PR) and minimal residual disease (MRD) and overall survival (OS), disease free survival (DFS) and event free survival were observed in 49 out of 78 trials. Other safety related endpoints apart from MTD and DLT were observed in 42 out of 78 trials. Safety related endpoints observed in phase I studies included adverse events (AEs) and toxicity profiling, occurrence rates of specific AEs such as graft versus host disease and infections. Therapeutic dose determination for subsequent trials was observed in 9 trials, out of which 7 trials specifically the recommended phase II dose (RP2D) endpoint. Eighteen trials measured drug pharmacokinetics while 9 trials measured different pharmacodynamic endpoints. Other endpoints observed in phase I trials included biomarker analysis, rate of successful manufacture for ATMPs, presence of human anti-murine antibodies, treatment compliance, palatability and acceptance of the different formulations.

Thirty phase I/II trials were analysed for choice of primary endpoints and number of endpoints studied. The average number of endpoints investigated in phase I/II trials was 3.2 and the mode was 3 endpoints. The most frequent endpoint was maximum tolerated dose which was observed in 8 trials. The second most frequent endpoint was overall survival (OS) and dose limiting toxicity (DLT) which were observed in 7 trials. The third most frequent endpoint was disease free survival which was observed in 5 trials.

Eighty-three phase II and phase II/III trials were analysed for choice of primary and secondary endpoints and number of endpoints, after 2 trials that lacked information on trial endpoints were excluded. The number of endpoints studied in phase II and phase II/III trials varied from a single endpoint up to 13 endpoints. The average number of endpoints investigated was 5.1 and the median was 5 endpoints.

The most frequent endpoints were OS observed in 30 out of 83 of trials, acute graft versus host disease (aGVHD) observed in 26 trials, chronic graft versus host disease (cGVHD) observed in 21 trials, EFS observed in 18 trials, MRD observed in 16 trials and treatment related mortality (TRM) observed in 15 trials. Other frequently observed endpoint groups in phase II and phase II/III trial were general safety related endpoints such as toxicity, tolerability and AEs characterisation were observed in 34 trials and relapse related endpoints such as relapse rate or incidence of relapse and relapse free survival were observed in 24 trials.

Endpoints used in trials investigating products for ALL and HSCT were also analysed separately. The most frequently observed endpoints in phase II and phase II/III studies are presented in Table 3-13 according to the trials area. Phase II and phase II/III studies consisted of 41 trials for HSCT and 42 trials for ALL.

Table 3-13: Frequently observed endpoints in phase II and phase II/III trials according to the respective trial area

Area			
HSCT (n = 41 trials)		**ALL (n = 42 trials)**	
Endpoint	**Number of trials (%)**	**Endpoint**	**Number of trials (%)**
aGVHD	26 (63%)	General safety related endpoints	26 (62%)
cGHVD	21 (51%)	MRD	16 (38%)
OS	17 (41%)	EFS	15(36%)
Engraftment	17 (41%)	OS	15(36%)
TRM	15 (37%)	PK	13(31%)
Graft failure	12 (29%)	CR related endpoints	12(29%)
Relapse related endpoints	11 (27%)	ORR	9 (21%)
NRM	10 (24%)	DLT & MTD	6 (14%)
DFS	9 (22%)	Patient successfully bridged to transplant	7 (17%)
General Safety related endpoints	7(17%)	Relapse related endpoints	5 (12%)
Chimerism	8 (20%)	PFS	2 (5%)
PFS	6 (15%)	DFS	2 (5%)

Abbreviations: aGVHD - Acute Graft versus Host Disease, cGHVD - Chronic Graft versus Host Disease, CR -Complete Remission, DFS - Disease-free survival, DLT - Dose limiting toxicities, EFS - Event-free survival, MRD - Minimal Residual Disease, MTD - Maximum Tolerated Dose, NRM - Non-relapse mortality, ORR Overall Remission Rate, OS - Overall Survival, PFS - Progression free survival, PK - Pharmacokinetics, TRM - Transplant Related Mortality,

Eighteen phase III trials were analysed for choice of primary and secondary endpoints and number of endpoints investigated. The number of endpoints studied in phase III trials varied from a single endpoint up to 15 endpoints. The average number of endpoints investigated was 5.6 and the median was 4 endpoints.

The most frequent single endpoints were EFS, MRD and OS which were observed in 9 out of 18 phase III trials. General safety related endpoints such as toxicity, tolerability and AEs characterisation were observed in 14 trials while 7 out of 18 trials used specified adverse events as study endpoints. The most frequent specific AE used as an endpoint was aGVHD that was observed in 3 out of 18 trials and in 3 out of the 4 trials

investigating product for HSCT. Two trials measured the incidence of new malignancies or secondary malignancies. Two out of 3 trials investigating a biological product measured drug antibody formation as an endpoint. Cytokine release syndrome was investigated specifically in a tisagenlecleucel safety study. Other frequently used endpoints in phase III trials were relapse related endpoints such as relapse rate/incidence and relapse free survival were observed in 6 out of 18 trials and disease-free survival was observed in 4 trials. Other endpoints of note were overall children development following exposure to chimeric antigen receptor T-cells and the use of a health-related quality of life (HRQOL) assessment following HSCT using allogeneic, umbilical cord blood-derived, ex vivo-expanded, haematopoietic CD133+ cells in place of stem cells derived from a donor.

3.2.2.5 Trial Design

The most frequent study design in phase I trials was the single group, open label (unblinded) trial observed in 38 out of 78 trials followed by non-randomized, single group, open label trials (n =12). Most phase I trials were unblinded with 65 out of 78 trials being described as open label trials. Parallel assignment was observed in 4 studies when compared to 50 single arm trials. Two trials were controlled and only one trial (EudraCT 2009-012718-35) was randomised. Trial EudraCT 2009-012718-35 was a BE study comparing the pharmacokinetics of two different formulations.

The most frequent study design in phase I/II trials was the single group, open label trial observed in 12 out of 30 trials followed by non-randomized, single group, open label trial (n = 5). Most phase I/II trials were also unblinded with 25 out of 30 trials being described as open label trials. Parallel assignment was observed in 2 studies when

compared to 17 single arm trials. A control group was included in 2 trials and no trials were described as randomised.

Prior to trial design analysis of phase II and phase II/III trials, one trial that lacked information on trial design was excluded. The most frequent study design in phase II and phase II/III trials was the single group, open label trial observed in 31 out of 84 trials followed by non-randomized, open label, parallel group trial (n = 8) and non-randomized, open label, single group trials (n = 7). The following trail design features in phase II and phase II/III trials were observed in the following frequencies; 69 out of 84 trials were open label, 41 were single group trials, 14 had parallel assignment, 6 were randomised, 3 had cross over assignment and 3 were blinded.

The most frequent trial design in phase III trials was the randomized, open label, parallel assignment trial that was observed in 4 out of 18 trials. When considering individual design features; 16 out of 18 trials were open label trials, 14 were randomised, 10 were controlled trials including one trial which was a historically controlled trial, 9 trials had parallel assignment and 1 trial was blinded.

3.3 Products in Prospective treatment protocols

The products in 65 phase II, phase II/III and phase III trials out of 227 total trials were used to propose prospective treatment protocols. One hundred sixty-two trials were excluded because they were; terminated (n = 25), initiated prior to November 2007 (n = 79), were in phase I, phase I/II or were BE studies (n = 52) and in 4 trials, the trial phase was not provided.

An additional 3 trials were excluded because of conflicting data or missing information. Trial NCT01990807 was excluded because conflicting data was observed in the study

record. Trials EudraCT 2012-003902 and EudraCT 2016-000297-38 were excluded because no information on how the investigational medicinal products (IMPs) were used to treat patients was present. Trial EudraCT 2012-003902 was a phase IV trial with a roll-over protocol to allow patients enrolled in past Novartis sponsored oncology studies to continue benefiting from treatment with nilotinib. EudraCT 2016-000297-38 was a long term follow up study to evaluate the long-term safety of patients with advanced lymphoid malignancies who had been administered with UCART19 in previous trials.

The 65 clinical trials used to propose prospective treatment protocols investigated 35 different products, 17 of which were small molecules including 2 novel liposomal formulations, 9 were ATMPs of which 4 were gene therapy medicinal products and 5 were somatic cell therapy medicinal product, 7 were biologicals of which 2 were novel pegylated or erythrocyte encapsulated formulations and 2 were antibody drug conjugates. An additional 6 products/indications which were described in PIPs were added to prospective treatment protocols. Prospective products used to propose treatment protocols are listed in Table 3-14 to Table 3-17.

Table 3-14: List of small molecules incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NCT Number
6-thioguanine (Guanosine analogue antimetabolite)	6-Thioguanine in combination with methotrexate (MTX) and mercaptopurine (6MP) during maintenance therapy	First line	EudraCT 2014-002248-42
Alisertib (Selective aurora A kinase inhibitor)	Single agent Alisertib for relapse/ refractory (r/r) ALL	Second line	NCT01154816
Allopurinol (Xanthine oxidase inhibitor)	Allopurinol combined with 6MP during maintenance therapy	First line	NCT03022747
Bortezomib (Proteasome inhibitor)	Bortezomib with combination chemotherapy	First line	NCT02112916, NCT03117751
		Second line	EudraCT 2009-014037-25, EudraCT 2012-000810-12, NCT00873093
Clofarabine (Purine nucleoside antimetabolite)	Clofarabine with combination chemotherapy	First line	EudraCT 2009-012758-18, EudraCT 2014-001866-90
		Second line	EudraCT 2009-012437-30, EudraCT 2011-004893-28, NCT01700946

Table 3-14: List of small molecules incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NCT Number
Dasatinib (Tyrosine kinase inhibitor)	Dasatinib with combination chemotherapy for newly diagnosed Ph+ ALL or r/r Ph+ ALL	First line	EudraCT 2010-022946-25, EudraCT 2011-001123-20, NCT00720109, NCT03020030, NCT02883049, NCT03117751
		Second line	EMEA-000567-PIP01-09-M04
DEPOCYT - Liposomal cytarabine (Nucleoside analogue antimetabolite)	Intrathecal (IT) DepoCyt during maintenance therapy for high risk (HR) ALL to replace six doses of conventional triple IT therapy	First line	EudraCT 2008-003235-20
Fludarabine (Purine analogue antimetabolite)	Fludarabine in combination with other agents with or without total body irradiation (TBI) as conditioning prior to HSCT	HSCT	EudraCT 2012-003032-22, NCT00448201, NCT01251575, NCT01527045, NCT01529827, NCT00914940, NCT01858740, NCT02220985, NCT00732316, NCT01028716
Forodesine (synthetic high-affinity transition-state analogue)	Forodesine monotherapy in children with relapsed/refractory haematological malignancies	Second line	EudraCT 2008-002219-42
Lestaurtinib (FLT3-selective tyrosine kinase inhibitor)	Lestaurtinib with combination chemotherapy for Infants (< 1 year) with ALL	First line	NCT00557193

Table 3-14: List of small molecules incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NCT Number
Momelotinib (Janus kinase inhibitor)	Momelotinib plus chemo for *de novo* ALL with Janus kinase (JAK) activating mutation	First line	EMEA-001656-PIP01-14
Crenigacestat (Notch I inhibitor)	Crenigacestat (LY3039478) in combination with Dexamethasone in T-ALL/ T- lymphoblastic lymphoma patients	Second line	EudraCT 2014-005024-10
Ponatinib (Tyrosine kinase inhibitor)	Ponatinib with chemotherapy for r/r Ph+ ALL	Second line	EMEA-001186-PIP01-11-M01
Pentoxifylline (Methylxanthine derivative)	Pentoxifylline versus placebo administered as apoptosis inductor during remission induction phase with chemotherapy for newly diagnosed ALL	First line	NCT02451774
Ruxolitinib (JAK1/JAK2 Inhibitor)	Ruxolitinib with combination chemotherapy for HR Ph-like B-ALL	First line	NCT02723994, NCT03117751
Treosulfan (Alkyl sulfonate)	Treosulfan in combination with other agents with or without TBI as conditioning prior to HSCT	HSCT	EudraCT 2011-001534-42, EudraCT 2013-003604-39 NCT00796068, NCT00860574

Table 3-14: List of small molecules incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NCT Number
MARQIBO - Liposomal Vincristine (Vinca alkaloid)	Panobinostat, bortezomib and liposomal vincristine for re-induction therapy for relapsed paediatric T-ALL	Second line	NCT02518750
Nelarabine (Purine nucleoside antimetabolite)	Nelarabine with combination chemotherapy	First line	EudraCT 2009-012758-18
Navitoclax (BCL-2 inhibitor)	Navitoclax alone or chemotherapy for r/r ALL	Second line	EMEA-000478-PIP01-08-M01

Table 3-15: List of antibody drug conjugates incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NCT Number
Coltuximab ravtansine (anti-CD19 antibody-maytansine conjugate)	Single agent coltuximab ravtansine for r/r ALL	Second-line	EudraCT 2012-002961-36
Inotuzumab Ozogamicin (anti-CD22 antibody - calicheamicin conjugate)	Inotuzumab alone for CD22-positive r/r ALL	Second line	NCT02981628

Table 3-16: List of advanced therapy medicinal products incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NTC Number
NiCord (*Ex vivo* expanded cell graft derived from umbilical cord stem cells)	NiCord vs unmanipulated umbilical cord blood for patients with haematological malignancies	HSCT	EudraCT 2014-000074-19, EudraCT 2015-004813-26, EudraCT 2016-000704-28
StemEx - Carlecortemcel-L (Graft of stem/progenitor cells isolated and expanded from umbilical cord blood)	Transplantation of StemEx in patients with HR haematological malignancies	HSCT	EudraCT 2006-005159-14
BPX-501 with CaspaCIDe T cells (CAR T-cells)	BPX -501 after mismatched, T depleted allo-transplantation in patients with haematological malignancies	HSCT	EudraCT 2014-000584-41
CD19ζ chimeric antigen receptor gene-modified EBV-specific CTLs (CAR T-Cells)	CD19 transduced EBV-CTL In CD19+ precursor B – ALL patients after undergoing allogeneic HSCT	HSCT	EudraCT 2007-007612-29
CD25/71 allodepleted donor T cells (Donor Lymphocyte infusion)	CD25/71 allodepleted donor T-cells to improve T-cell reconstitution after allogeneic HSCT	HSCT	EudraCT 2013-000872-14
Off-the-Shelf Expanded Cord Blood Cells	Intravenous (IV) *ex vivo*-expanded cord blood progenitor cells given after unmanipulated umbilical chord blood (UCB)	HSCT	NCT01175785

Table 3-16: List of advanced therapy medicinal products incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed line of therapy / Area	EudraCT Number or NTC Number
Mesenchymal stem cells (MSC)	Co-transplantation of MSC to support HSCT	HSCT	EudraCT 2008-005594-35, EudraCT 2009-011817-26
Tisagenlecleucel (CAR T-cell)	Tisagenlecleucel monotherapy for r/r B-ALL patients	Second Line	EudraCT 2013-003205-25, EudraCT 2014-001673-14, EudraCT 2015-003736-13, EudraCT 2016-001991-31, EudraCT 2017-002849-30
MM-TK donor lymphocytes (Donor Lymphocyte infusion)	MM-TK (MolMED-Thymidine kinase) donor lymphocytes vs standard strategy in HR ALL paediatric patients undergoing HSCT.	HSCT	EMEA-001370-PIP02-13
ATIR101 (Donor Lymphocyte Infusion)	ATIR101 administered as an adjunctive immunotherapeutic on top of HSCT	HSCT	EudraCT 2015-002821-20, EudraCT 2016-004672-21
KTE-C19 (CAR T-cell)	KTE C19 for r/r B-ALL.	Second line	EMEA-001862-PIP01-15

Table 3-17: List of biologicals incorporated into proposed prospective treatment protocols

Active Substance (Drug Class)	Trial Description	Proposed Line of therapy / Area	EudraCT Number or NTC Number
Rituximab (Anti-CD20 monoclonal antibody)	Randomised administration of a dose of rituximab prior first pegaspargase dose to prevent sensitization in patients with B-ALL	First line	NCT03117751
Rituximab (Anti-CD20 monoclonal antibody)	Pre- and Post-Transplant Rituximab for patient with r/r CD20+ B-ALL	HSCT	NCT00867529
Blinatumomab (Bispecific T cell engager (BiTE) antibody)	Blinatumomab as consolidation therapy vs conventional consolidation chemotherapy in relapsed HR B-ALL	Second line	EudraCT 2010-024264-18, EudraCT 2014-001700-21, EudraCT 2014-002476-92, EudraCT 2016-004674-17
Epratuzumab (Humanized anti-CD22 monoclonal antibody)	Consolidation with epratuzumab and chemotherapy in standard risk (SR) relapsed ALL	Second line	EudraCT 2012-000793-30
GRASPA - L-asparaginase encapsulated in erythrocytes (Asparagine depleting Enzyme)	GRASPA versus reference L-asparaginase treatment in combination with chemotherapy for ALL	First line	EudraCT 2009-012584-34, EudraCT 2016-004451-70
Moxetumomab Pasudotox (Anti-CD22 immunotoxin)	Moxetumomab Pasudotox for r/r ALL	Second line	EudraCT 2012-003101-10
Calaspargase Pegol (Asparagine depleting Enzyme)	Randomized study of Calaspargase Pegol (SC-PEG) vs. Oncaspar	First line	NCT01574274

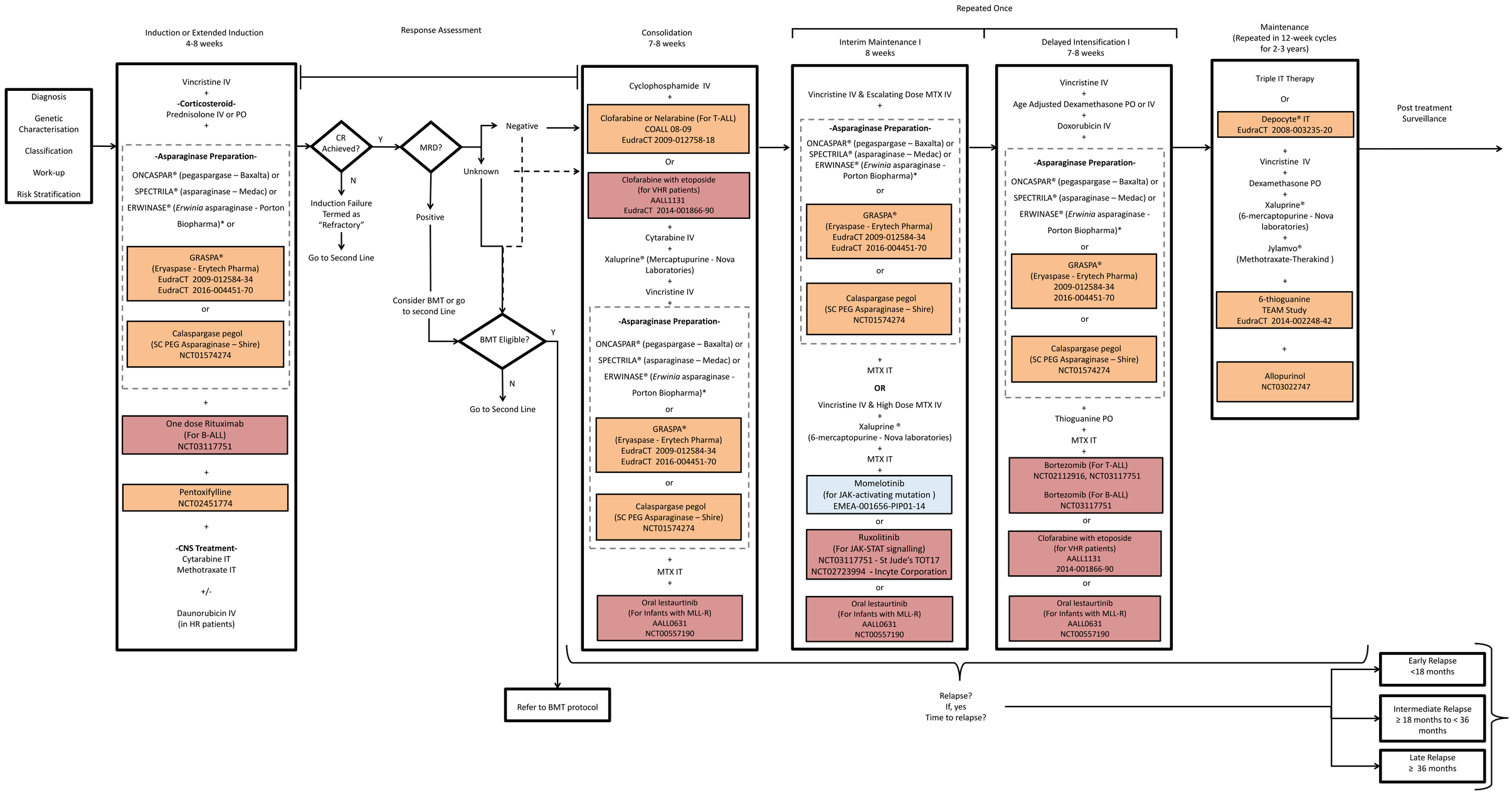
3.3.1 Proposed prospective treatment protocols and product review

Five prospective treatment protocols were proposed for (i) first line Philadelphia chromosome negative B-ALL or T-ALL (Figure 3-7), (ii) second line Philadelphia chromosome negative B-ALL or T-ALL (Figure 3-8), (iii) bone marrow transplantation (Figure 3-9), (iv) first line Philadelphia chromosome positive ALL (Figure 3-10) and (v) second line Philadelphia chromosome positive ALL (Figure 3-11).

The proposed first line prospective treatment protocols for Philadelphia chromosome negative (Ph-) B-ALL or T-ALL is based on the COGALL0232 and COGAALL0434 treatment protocols. Patients who do not achieve complete remission or who have positive minimal residual disease are proposed to be treated with a second line protocol or with HSCT. Second line treatment options are varied and depend on risk stratification and clinical judgement. HSCT can be also be considered after second line treatment failure. A second allogeneic HSCT and/or donor lymphocyte infusion (DLI) can be considered for patients with relapsed disease after first allogeneic HSCT. The proposed first line prospective treatment protocols for Philadelphia positive is based on COGAALL0031. Philadelphia positive patients who experience induction failure can be treated a second line treatment protocol. Patients who achieve complete remission can be offered HSCT if they are eligible. Patients who are not eligible for HSCT should continue with multiagent chemotherapy with a tyrosine kinase inhibitor such as imatinib or dasatinib. Second line treatment options for Ph- ALL include combination chemotherapy or monotherapy with a biological or a Chimeric Antigen Receptor T Cells (CAR-T) based ATMP. The preferred second line treatment options for Philadelphia positive ALL is multiagent chemotherapy with a different tyrosine kinase inhibitor not used as a first line agent and monotherapy with a biological or a CAR-T based ATMP may be offered to patients who fail two tyrosine kinase inhibitors (TKIs).

Figure 3-7: Schematic representation of a prospective first-line treatment protocol for Philadelphia negative high-risk B-cell or T-cell ALL

Based on COGALL0232 and COGAALL0434 for T-ALL. Other treatment protocols may be used as first line regimens as per NCCN ALL guidelines for 2017



Legend

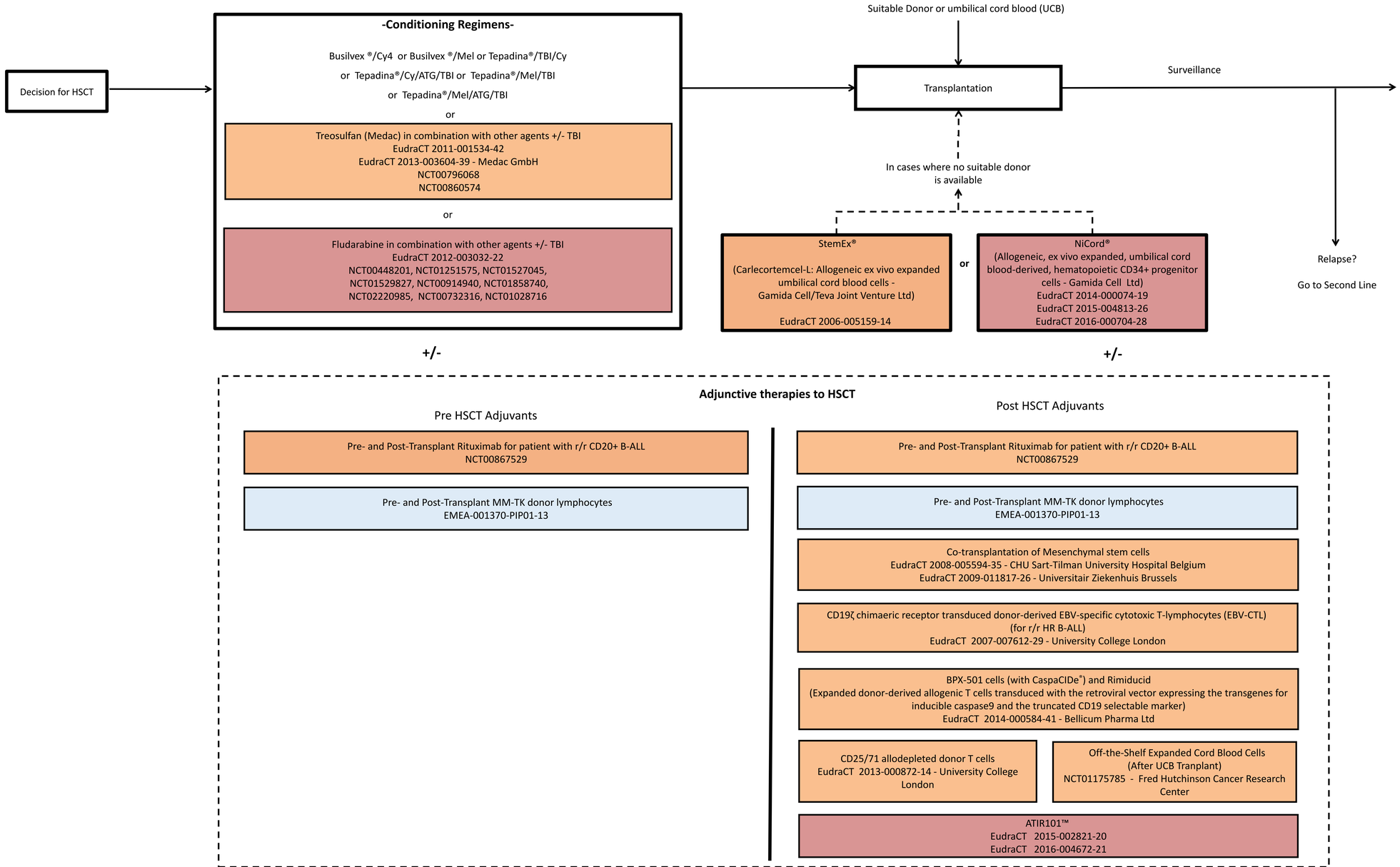
Highest Phase of Development — Phase II — Phase III — PIPs — Drugs with same role/category

*In patients who develop hypersensitivity to L-asparaginase from *Escherichia coli*

Abbreviations: BMT – Bone Marrow transplantation, CNS – Central Nervous System, CR – Complete Remission, HR – High Risk, IT – Intrathecal, IV - Intravenous, JAK – Janus Kinase, MLL-R - Mixed Lineage Leukaemia Rearrangements, MRD - Minimal residual disease, MTX – methotrexate, N – No, PIPs – Paediatric Investigation Plans, PO – Oral, STAT - Signal Transducer and Activator of Transcription protein, VHR – Very High Risk, Y – Yes.

Figure 3-8: Schematic representation of the bone marrow transplantation (Allogenic HSCT) procedure

HSCT can be considered after first line induction failure or relapse or after second line treatment failure. A second allogeneic HSCT and/or donor lymphocyte infusion (DLI) can be considered for patients with relapsed disease after first allogeneic HSCT



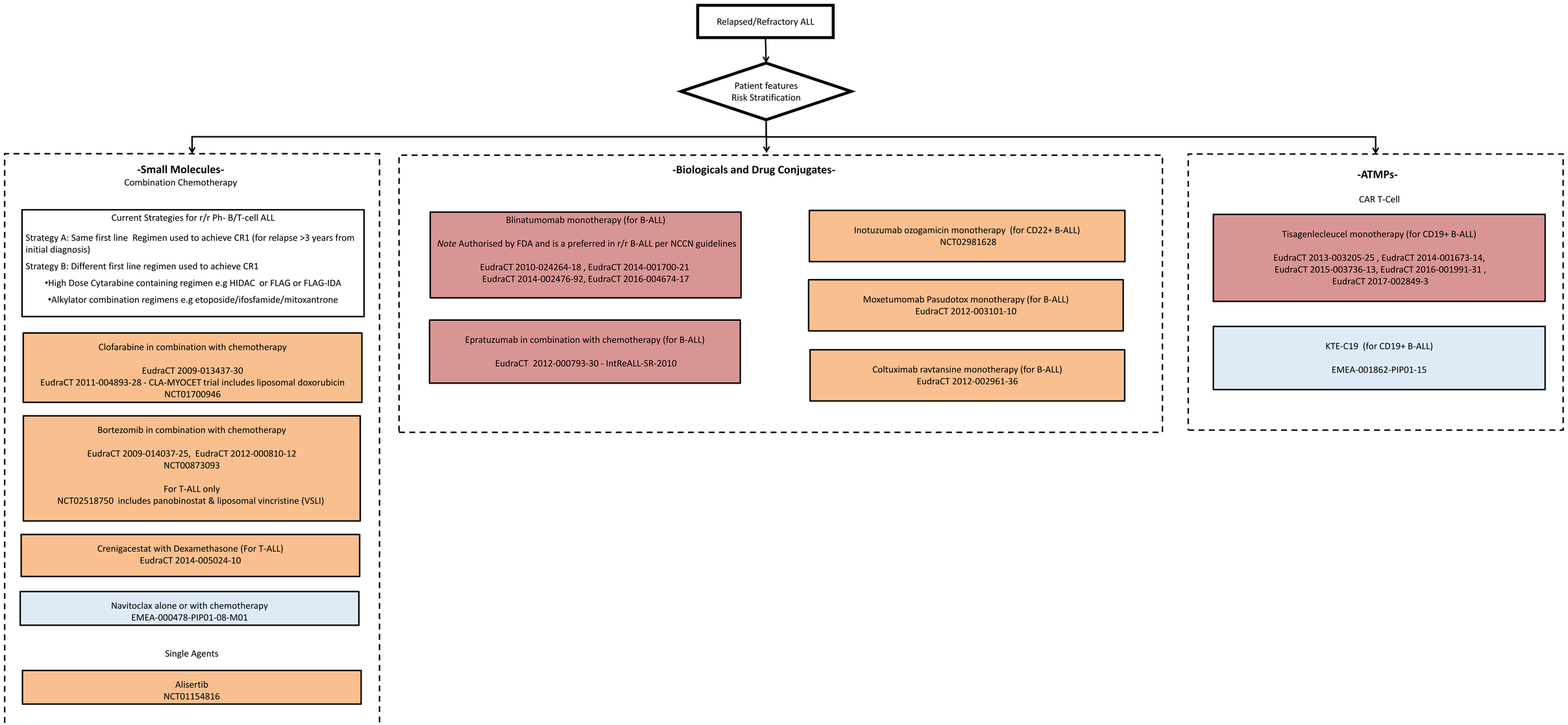
Legend

Highest Phase of Development — Phase II — Phase III — PIPs — Drugs with same role/category

Abbreviations: ATG - Antithymocyte globulin, BMT – Bone Marrow transplantation, Cy – Cyclophosphamide .DLI - Donor Leukocyte Infusion .EBV - Epstein-Barr Virus, HSCT - Hematopoietic stem cell transplantation, Mel – Melphalan, MM-TK – MolMED Thymidine kinase, HR – High risk, N – No, PIP – Paediatric Investigation Plans, r/r – relapsed/refractory .TBI – Total Body Irradiation .UCB – Umbilical Cord Blood, Y - Yes

Figure 3-9: Schematic representation of prospective second-line treatment protocol for Philadelphia negative high-risk B-cell or T-cell ALL

Second line Treatment options are varied and depend on risk stratification and clinical judgement



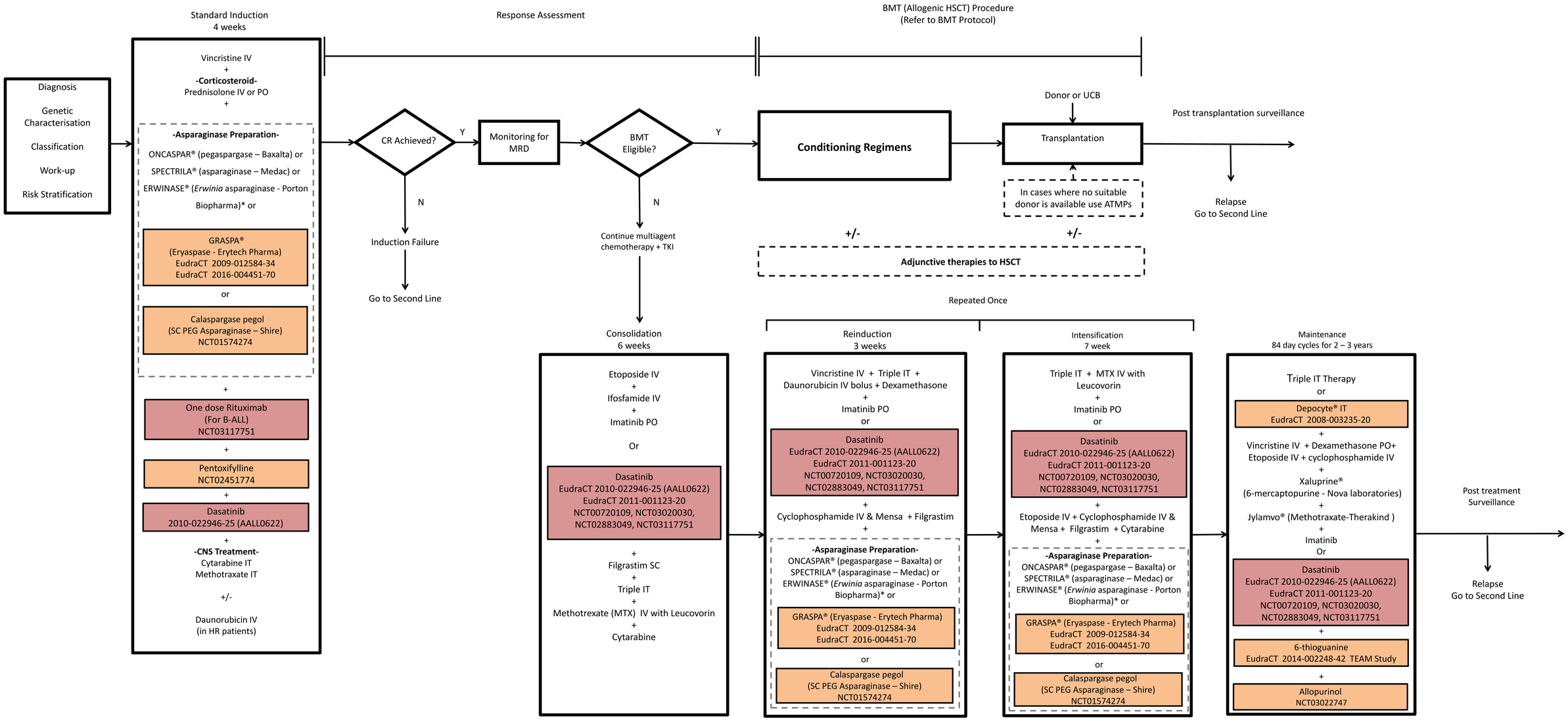
Legend

Highest Phase of Development — Phase II — Phase III — PIP — Drugs with same role/category

Abbreviations:, CAR - Chimeric antigen receptor, CR1 – First Complete Remission, FDA – Food and Drug Administration, FLAG - **F**ludarabine, cytarabine (**A**ra-C) and filgrastim (**G**-CSF), FLAG-IDA - **F**ludarabine, cytarabine (**A**ra-C), filgrastim (**G**-CSF) and **Ida**rubicin, HIDAC - High Dose Ara-C, NCCN – National Comprehensive Cancer Network, PIPs – Paediatric Investigation Plans, r/r – relapsed/refractory, VSLI - Vincristine Sulfate Liposome Injection.

Figure 3-10: Schematic representation of proposed prospective first line treatment protocol for Philadelphia positive B-cell ALL

Based on COGAALL0031. Other treatment protocols may be used as first line regimens as per NCCN ALL guidelines for 2017



Legend

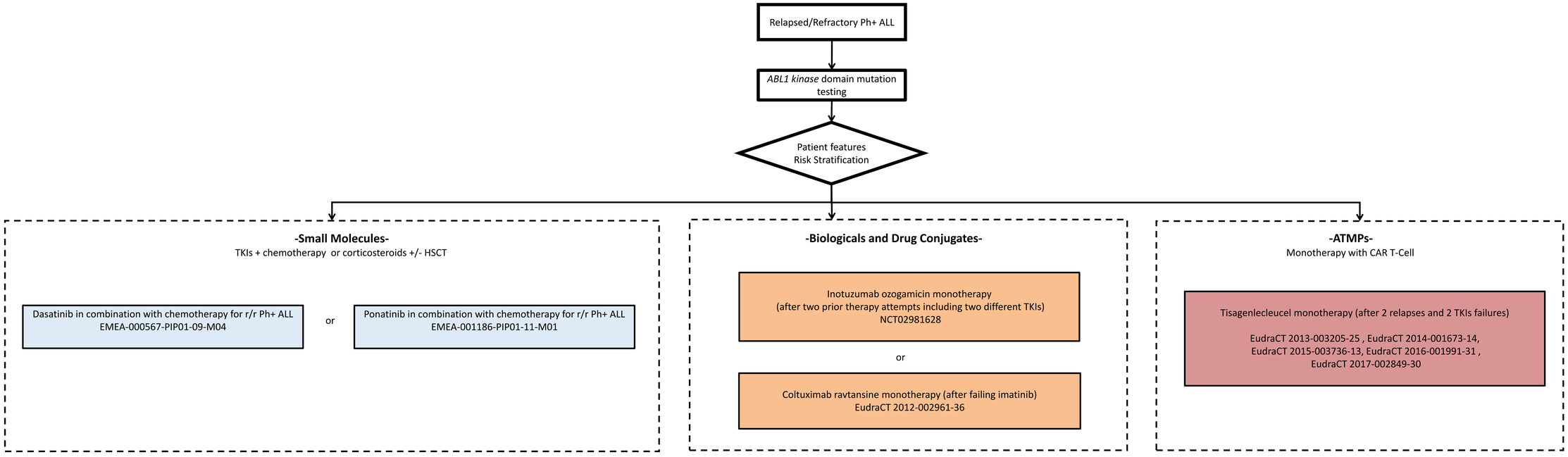
Highest Phase of Development — Phase II — Phase III — Drugs with same role/category

•*In patients who develop hypersensitivity to L-asparaginase from *Escherichia coli*

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, ATMP – Advanced therapy medicinal product, BMT – Bone Marrow transplantation, CNS – Central Nervous System, CR – Complete Remission, HR – High Risk, IT – Intrathecal, IV - Intravenous, MRD - Minimal residual disease, MTX – methotrexate, N – No, Ph – Philadelphia chromosome, PIPs – Paediatric Investigation Plans, PO – Oral, TKI – Tyrosine Kinase Inhibitor, UCB – Umbilical Cord Blood, Y – Yes.

Figure 3-11: Schematic representation of proposed prospective second line treatment protocol for Philadelphia positive B-cell ALL

Second line Treatment options are varied and depend on risk stratification and clinical judgement



Legend

Highest Phase of Development — Phase II — Phase III — PIP — Drugs with same role/category

Abbreviations: ALL – Acute Lymphoblastic Leukaemia, CAR – Chimeric Antigen Receptor, HSCT – Haematopoietic stem cell transplantation, Ph+ – Philadelphia chromosome positive, PIPs – Paediatric Investigation Plans, r/r – relapsed/ refractory, – Tyrosine Kinase Inhibitor.

3.3.1.1 Prospective First line Philadelphia negative ALL treatment protocol

Thirteen prospective products were proposed to have a first line indication for Philadelphia negative B or T cell ALL (Table 3-18). Ten of the prospective first line products were small molecules and 3 were biologicals.

Table 3-18: Products were proposed to have a first line indication for Philadelphia negative B or T cell ALL

Active Substance (Drug Class)	Drug Category	Trial Description	EudraCT Number or NCT Number
6-thioguanine (Guanosine analogue antimetabolite)	Small Molecule	6-Thioguanine in combination with MTX and 6MP during maintenance therapy	EudraCT 2014-002248-42
Allopurinol (Xanthine oxidase inhibitor)	Small Molecule	Allopurinol combined with 6MP during maintenance therapy	NCT03022747
Bortezomib (Proteasome inhibitor)	Small Molecule	Bortezomib with combination chemotherapy	NCT02112916, NCT03117751
Calaspargase Pegol (Asparagine depleting Enzyme)	Biological	Randomized study of Calaspargase Pegol (SC-PEG) vs. Oncaspar	NCT01574274
Clofarabine (Purine nucleoside antimetabolite)	Small Molecule	Clofarabine with combination chemotherapy	EudraCT 2009-012758-18, EudraCT 2014-001866-90
DEPOCYT - Liposomal cytarabine (Nucleoside analogue antimetabolite)	Small Molecule	IT DepoCyt during maintenance therapy for HR-ALL to replace six doses of conventional triple IT therapy	EudraCT 2008-003235-20
GRASPA - L-asparaginase encapsulated in erythrocytes (Asparagine depleting Enzyme)	Biological	GRASPA versus reference L-asparaginase treatment in combination with chemotherapy for ALL	EudraCT 2009-012584-34, EudraCT 2016-004451-70
Lestaurtinib (FLT3-selective tyrosine kinase inhibitor)	Small Molecule	Lestaurtinib with combination chemotherapy for Infants (< 1 year) with ALL	NCT00557193
Momelotinib (Janus kinase inhibitor)	Small Molecule	Momelotinib plus chemo for *de novo* ALL with JAK- activating mutation	EMEA-001656-PIP01-14
Nelarabine (Purine nucleoside antimetabolite)	Small Molecule	Nelarabine with combination chemotherapy	EudraCT 2009-012758-18
Pentoxifylline (Methylxanthine derivative)	Small Molecule	Pentoxifylline versus placebo administered as apoptosis inductor during remission induction phase with chemotherapy for newly diagnosed ALL	NCT02451774
Rituximab (Anti-CD20 monoclonal antibody)	Biological	Randomised administration of a dose of rituximab prior first pegaspargase dose to prevent sensitization in patients with B-ALL	NCT03117751
Ruxolitinib (JAK1/JAK2 Inhibitor)	Small Molecule	Ruxolitinib with combination chemotherapy for HR Ph-like B-ALL	NCT02723994, NCT03117751

Two novel forms of the asparaginase enzyme are in development and were proposed as component of induction and consolidation treatment phases. Graspa is the propriety name given to eryaspase, which is L-asparaginase encapsulated in erythrocytes, and is currently being developed by Erytech Pharma SA. Erytech Pharma SA uses its proprietary Erycaps platform to encapsulate drug substances into red blood cells[32]. The hypothesis behind encapsulation in a red blood cell membrane is to prolong the circulation time and to reduce toxicity and hypersensitivity. Graspa is currently in phase II/III development with 2 registered clinical trials for patients with relapsed or refractory (r/r) ALL (EudraCT 2009-012584-34) and newly diagnosed (*de novo*) ALL for patient with hypersensitivity to peg-asparaginase (EudraCT 2016-004451-70).

Calaspargase pegol (SC-PEG) is another new formulation of the asparaginase enzyme that is being developed by Shire Plc[33]. This product is identical to Oncaspar (SS-PEG) except for a succinimidyl carbonate linker, a more hydrolytically stable linker moiety, that replaces the succinimidyl succinate linker found in Oncaspar (Angiolillo et al, 2014). Calaspargase pegol is being studied in a phase II randomised controlled trial with Oncaspar as its active comparator. The main objective of the trial is to study and compare the pharmacokinetic and safety profile of SC-PEG.

Pentoxifylline and rituximab were proposed as add on treatment to induction therapy. Both are established products although none have an ALL indication. The safety and efficacy of pentoxifylline versus placebo administered as apoptosis inductor during remission induction phase is being investigated in NCT02451774. Pentoxifylline is a methylxanthine derivative that acts as a non-specific phosphodiesterase inhibitor

[32] Erytech Pharma SA. About Erytech (Online). Lyon(FR): Erytech Pharma; c2016 [cited 2018 Mar 15]. Avialable from URL: http://erytech.com/about.html
[33]Shire. ClinicaL Programs in Pipeline (Online). Dublin (IE): Shire plc; c2018 [cited 2018 April 8]. Avialable from URL: https://www.shire.com/research-and-development/pipeline

(Marcinkiewicz et al, 2000). The current indication of pentoxifylline is for the treatment of peripheral vascular disease, including intermittent claudication and rest pain[34]. The investigators hypothesis is that adding pentoxifylline to the induction phase will optimise the antineoplastic effect of treatments, resulting in an increase in the apoptosis of leukemic cells.

Total Therapy XVII (TOT17) is registered in clinicaltrials.gov as NCT03117751 and is sponsored by St. Jude Children's Research Hospital[35]. TOT17 aims to maximise the survival of newly diagnosed patients with ALL and lymphoma. Innovative therapeutic approaches are investigated in 8 treatment arms. One trial arm aims to examine whether the administration of one dose of rituximab to children with B-ALL during early induction therapy decreases allergic reactions to pegaspargase. Rituximab is a chimeric anti-human CD20 monoclonal antibody (mAbs) with a diverse mechanism of action (Pescovitz, 2006). Cited literature maintains that rituximab has direct effects that include complement-mediated cytotoxicity and antibody-dependent cell-mediated cytotoxicity, and indirect effects that include structural changes, apoptosis, and sensitisation of cancer cells to chemotherapy (Cerny et al, 2002; Jazirehi & Bonavida, 2005; Weiner, 2010). Rituximab is currently only indicated for adults with non-Hodgkin lymphoma, chronic lymphocytic leukaemia, rheumatoid arthritis and granulomatosis with polyangiitis and microscopic polyangiitis although paediatric off-label use is known (Aguiar et al, 2014; Dale et al, 2014). Rituximab has also been investigated in other B cell malignancies (Barth et al, 2013).

[34] Electronic Medicines Compendium. Summary of Product Characteristic for Trental 400 (Online). Surrey (UK): Datapharm Communications Limited; c2018 [Updated 2016 Aug 23: cited 2018 Feb 17]. Available from URL: https://www.medicines.org.uk/emc/product/909/smpc

[35]St. Jude Children's Research Hospital. Total Therapy Study 17 for Newly Diagnosed Patients with Acute Lymphoblastic Leukemia and Lymphoma (Online). Memphis (TN): St. Jude Children's Research Hospital; c2018 [cited 2018 Feb 17]. Available from URL: https://www.stjude.org/research/clinical-trials/tot17-leukemia-lymphoma.html

Six products, clofarabine, nelarabine, lestaurtinib, momelotinib, ruxolitinib and bortezomib, are being investigated as part of multiagent chemotherapy given during the consolidation phase. All 6 products are small molecules.

Clofarabine is being investigated as part of multiagent chemotherapy in two trials, EudraCT 2009-012758-18 and 2014-001866-90. Clofarabine is a purine nucleoside antimetabolite (Pui & Jeha, 2005) developed by Genzyme that was granted a MA in the EU under exceptional circumstances as third line monotherapy for ALL. Both trials are being sponsored by large study groups. EudraCT 2009-012758-18 (COALL09-05-04) is a phase II trial sponsored by the German Society of Paediatric Haematology and Oncology while EudraCT 2014-001866-90 (AALL1131) is a phase III trial sponsored by the Children's Oncology Group. The aim of these trials is to investigate the effects of adding clofarabine to chemotherapy for newly diagnosed high risk B-Lymphoblastic Leukaemia (B-ALL). Preliminary results suggest that clofarabine combined with pegylated asparaginase is safe and effective in the frontline treatment of ALL (Escherich et al, 2013). COALL 08 09 also lists nelarabine in the study record and allows for recruitment of patients with T-ALL. Nelarabine is a purine nucleoside antimetabolite (Buie et al, 2007) developed by Glaxosmithkline and granted a MA under exceptional circumstances for third line monotherapy of T-ALL.

Lestaurtinib is a Feline McDonough Sarcoma (FMS)-like tyrosine kinase 3 (FLT3) inhibitor (Fathi & Levis, 2009) being investigated in NCT00557193, a phase III study for infants with mixed-lineage leukemia (MLL) rearranged ALL. The molecule was originally developed by Cephalon under the name CEP-701 and has since been acquired

by Teva[36] although no information on current commercialisation plans were found on Teva's website[37]. Trial NCT00557193 is sponsored by the Children's Oncology Group (AALL0631) and randomises high risk infants with MLL rearrangement to intensive chemotherapy with or without lestaurtinib.

Momelotinib is a Janus kinase (JAK) 1 and 2 inhibitor developed by Gilead Sciences International Ltd (Harrison et al, 2018). The PIP decision (P/0157/2015) for momelotinib includes a trial to evaluate the safety and efficacy of momelotinib as add on therapy for newly-diagnosed acute lymphoblastic leukaemia patients with JAK activating mutations. No clinical trials investigating momelotinib for ALL were retrieved, although 3 clinical trials for polycythaemia vera, essential thrombocythemia and myelofibrosis were registered. The PIP is expected to be completed by July 2027 indicating that the company is currently pursuing an indication in other conditions before initiating clinical trials in children with ALL.

Ruxolitinib is a JAK 1 and 2 inhibitor (Vannucchi et al, 2015) that is authorised in Europe for myeloproliferative disorders in adults as Jakavi[38]. Two trials, TOT17 (described above) and NCT02723994 sponsored by Incyte are investigating ruxolitinib in *de novo* ALL with JAK activating mutations. The hypothesis is that the addition of ruxolitinib in patients with a targetable genomic abnormality in the JAK/STAT pathway will improve overall treatment outcome in this patient cohort.

[36]Adis Insight. Drug Profile for Lestaurtinib (Online). Cham (CH) Springer International Publishing AG: c2016 [cited 2018 April 13]. Available from URL: https://adisinsight.springer.com/drugs/800010795

[37]Teva Pharmaceutical Industries Ltd. Our Specialty Pipeline (Online). Petah Tikva (IL): Teva Pharmaceutical Industries Ltd; c2017 [cited 2018 April 18]. Available from URL: http://www.tevapharm.com/research_development/rd_focus/pipeline/

[38]European Medicines Agency. Product Information for Jakavi - EMEA/H/C/002464 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 Sep 14; cited 2018 Mar 11]. Available from URL: http://www.ema.europa.eu/ema

Bortezomib is a proteasome inhibitor (Field-Smith et al, 2006) that is authorised in Europe for Multiple Myeloma in adults as Valcade[39]. Bortezomib is being investigated as add-on therapy for patients with T-ALL who have a poor early response to treatment but have no targetable lesions in two trials. Both trials are sponsored by international study groups; TOT17 (NCT03117751) sponsored by St Jude Research Hospital and NCT02112916 sponsored by the national cancer institute and is also known as Children's Oncology Group (COG) study AALL1231.

Three products were proposed for maintenance phase therapy in first line Ph- ALL. The Thiopurine EnhAnced Maintenance Therapy (TEAM) study (EudraCT 2014-002248-42), aims to explore the feasibility of adding tioguanine to maintenance therapy of acute lymphoblastic leukaemia and lymphoblastic non-Hodgkin's lymphoma. Tioguanine (6TG) is a sulfhydryl analogue of guanine and behaves as a purine antimetabolite. It is activated to its nucleotide, thioguanylic acid. Tioguanine metabolites inhibit *de novo* purine synthesis and purine nucleotide interconversions. Tioguanine is also incorporated into nucleic acids, and DNA (deoxyribonucleic acid) incorporation is claimed to contribute to the agent's cytotoxicity[40]. Investigators hypothesize that MTX/6MP/6TG combination therapy will achieve a higher DNA-TGN blood levels and enhance the cytotoxic effect of 6MP to reduce relapse rates.

[39]European Medicines Agency. Product Information for Valcade - EMEA/H/C/000539 -IB/0083 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 Mar 10; cited 2018 Mar 11]. Available from URL: http://www.ema.europa.eu/ema

[40] Electronic Medicines Compendium. Summary of Product Characteristic for Tioguanine 40 mg Tablets (Online). Surrey (UK): Datapharm Communications Limited; c2018 [Updated 2017 Nov 22: cited 2018 Feb 17]. Available from https://www.medicines.org.uk/emc/product/4654/smpc

DepoCyte is a sustained-release formulation of cytarabine developed by MundiPharm and is designed for direct administration into the cerebrospinal fluid (CSF)[41]. DepoCyte is currently authorised for intrathecal treatment of lymphomatous meningitis in adults. Cytarabine is a cell-cycle phase specific antineoplastic agent, affecting cells only during the S-phase of cell division. Intracellularly, cytarabine is converted into cytarabine-5'-triphosphate (ara-CTP), which is the active metabolite. The mechanism of action is not completely understood, but it appears that araCTP acts primarily through inhibition of DNA synthesis. Incorporation into DNA (deoxyribonucleic acid) and RNA (ribonucleic acid) may also contribute to cytarabine cytotoxicity[36]. In NOPHO-ALL-2008 study (EudraCT 2008-003235-20) Rigshospitalet is investigating if replacing six doses of conventional triple intrathecal therapy (methotrexate, cytarabine and prednisolone) with DepoCyte during maintenance therapy for HR-ALL will yield an equal or reduced rate of serious toxicity with a similar or decreased CNS and overall relapse rate.

Trial NCT03022747 aims to investigate the potential optimisation of 6-mercaptopurine therapy with the addition of allopurinol as modifier. The trail involves adding allopurinol to the treatment regimen while simultaneously reducing 6MP. The rational is based on the well-known interaction whereby allopurinol increases levels of mercaptopurine by decreasing metabolism. Literature reports similar approaches in other conditions such as the use of allopurinol to optimize thiopurine immunomodulator efficacy in inflammatory bowel disease (Sparrow, 2008).

[41]European Medicines Agency. Product Information for DepoCyte -EMEA/H/C/000317 -N/0059 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 Aug 7; cited 2018 May 5]. Available from URL: http://www.ema.europa.eu/ema

3.3.1.2 Prospective Second line Philadelphia negative ALL treatment protocols

Twelve prospective products were proposed to have a second line indication for Philadelphia negative B or T cell ALL (Table 3-19). Five of the prospective second line products were small molecules, 3 were drug-conjugates, 2 were biological and 2 were ATMPs. Second line treatment protocols could be based on multiagent chemotherapy or on monotherapy with biologicals, ADCs, immunotoxins or ATMPS.

Small molecules clofarabine and bortezomib are being studied in combination with other agents in relapsed ALL patients. Both products have been discussed in Section 3.3.1.1. Two trials involving clofarabine and bortezomib are simultaneously investigating novel formulation of established agents. The CLA-MYOCET Trial (EudraCT number 2011-004893-28) is investigating clofarabine in combination with cytarabine and liposomal doxorubicin in children with leukaemia. Liposomal doxorubicin is authorised in the EU for breast neoplasms under the trade name Myocet (Liposome–encapsulated doxorubicin–citrate complex). In the overall management of breast cancer Myocet was proven to be a less cardiotoxic and better tolerated form of doxorubicin that was equally efficacious (Batist et al, 2002). Myocet has also been studied in combination with fludarabine with cytarabine and granulocyte colony-stimulating factor (FLAG)(Quarello et al, 2012).

Table 3-19: Products were proposed to have a second line indication for Philadelphia negative B or T cell ALL

Active Substance (Drug Class)	Drug Category	Trial Description	EudraCT Number or NCT Number
Alisertib (Selective aurora A kinase inhibitor)	Small Molecule	Single agent Alisertib for relapse/ refractory (r/r) ALL	NCT01154816
Blinatumomab (Bispecific T cell engager (BiTE) antibody)	Biological	Blinatumomab as consolidation therapy vs conventional consolidation chemotherapy in relapsed HR B-ALL	EudraCT 2010-024264-18, EudraCT 2014-001700-21, EudraCT 2014-002476-92, EudraCT 2016-004674-17
Bortezomib (Proteasome inhibitor)	Small Molecule	Bortezomib with combination chemotherapy	EudraCT 2009-014037-25, EudraCT 2012-000810-12, NCT00873093
Clofarabine (Purine nucleoside antimetabolite)	Small Molecule	Clofarabine with combination chemotherapy	EudraCT 2009-012437-30, EudraCT 2011-004893-28, NCT01700946
Coltuximab ravtansine (anti-CD19 antibody-maytansine conjugate)	ADC	Single agent coltuximab ravtansine for r/r ALL	EudraCT 2012-002961-36
Crenigacestat (Notch I inhibitor)	Small Molecule	Crenigacestat (LY3039478) in Combination with Dexamethasone in T-ALL/T-LBL Patients	EudraCT 2014-005024-10
Epratuzumab (Humanized anti-CD22 monoclonal antibody)	Biological	Consolidation with epratuzumab and chemotherapy in SR relapsed ALL	EudraCT 2012-000793-30
Forodesine (synthetic high-affinity transition-state analogue)	Small Molecule	Forodesine monotherapy in children with relapsed/refractory haematological malignancies	EudraCT 2008-002219-42
Inotuzumab Ozogamicin (anti-CD22 antibody - calicheamicin conjugate)	ADC	Inotuzumab alone for CD22-positive r/r ALL	NCT02981628
KTE-C19 (CAR T-cell)	ATMP	KTE C19 for r/r B-ALL.	EMEA-001862-PIP01-15
MARQIBO - Liposomal Vincristine (Vinca alkaloid)	Small Molecule	Panobinostat, Bortezomib and Liposomal Vincristine for re-induction therapy for relapsed paediatric T-ALL	NCT02518750
Moxetumomab Pasudotox (Anti-CD22 immunotoxin)	ADC	Moxetumomab Pasudotox for r/r ALL	EudraCT 2012-003101-10
Navitoclax (BCL-2 inhibitor)	Small Molecule	Navitoclax alone or chemotherapy for r/r ALL	EMEA-000478-PIP01-08-M01
Tisagenlecleucel (CAR T-cell)	ATMP	Tisagenlecleucel montherapy for r/r B-ALL patients	EudraCT 2013-003205-25, EudraCT 2014-001673-14, EudraCT 2015-003736-13, EudraCT 2016-001991-31, EudraCT 2017-002849-30

Abbreviations: ADC, Antibody-Drug Conjugate; ATMP, Advanced Therapy Medicinal Product.

In trail NCT02518750, investigators are studying the combination of panobinostat, bortezomib and liposomal vincristine (VSLI) as a strategy for re-induction for r/r T-ALL. Panobinostat and bortezomib are authorised in the EU for multiple myeloma in adults under the tradenames Farydak[42] and Velcade[39] respectively. Liposomal vincristine has an orphan designation (EU/3/08/555)[43] in the EU but is not authorised. Clinical trials in adults and adolescent and young adult (AYA) populations demonstrated better safety, tolerability, anti-tumour activity of VSLI when compared to vincristine (Silverman & Deitcher, 2013; Schiller et al, 2015). The FDA licensed VSLI for adults with relapsed or refractory ALL in 2012[44].

Crenigacestat (LY3039478) is a small molecule shown *in vitro* to inhibit the Notch signalling pathway and is being investigated by Eli Lilly and Company for T-ALL and T-cell lymphoblastic lymphoma (T-LBL) patients[45]. In trial 2014-005024-10, investigators are studying the potential of crenigacestat in combination with dexamethasone to induce remission in r/r T-ALL patients.

Navitoclax (ABT-263) is an orally active inhibitor of Bcl-2 (B-cell lymphoma 2) and apoptotic inhibitor Bcl-xL (B-cell lymphoma-extra-large) (Park et al, 2008; Tso et al, 2008). AbbVie Ltd applied for a PIP for Navitoclax for the treatment of

[39]European Medicines Agency. Product Information for Valcade - EMEA/H/C/000539 -IB/0083 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 Mar 10; cited 2018 Mar 11]. Available from URL: http://www.ema.europa.eu/ema

[42] European Medicines Agency. Product Information for Farydak - EMEA/H/C/003725 [Online]. London(UK): European Medicines Agency; c1995-2017 [updated 2017 Jul 5; cited 2018 Mar 15]. Available from URL: http://www.ema.europa.eu/ema

[43]European Medicines Agency. Orphan designation (EU/3/08/555) for vincristine sulphate liposomes for the treatment of acute lymphoblastic leukemia [Online]. London(UK): European Medicines Agency; c1995-2017 [cited 2018 Mar 17]. Available from URL: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/orphans/2009/11/human_orphan_000425.jsp&mid=WC0b01ac058001d12b

[44] Food and Drug Administration. Drug Approval Package for Marqibo (vinCRIStine sulfate LIPOSOME injection) [Online]. Rockville (MD): U.S. Department of Health and Human Services; c2007 [cited 2018 Mar 17]. Available from URL: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202497_marqibo_toc.cfm

[45] Eli Lilly and Company. Lilly Oncology Pipeline - Notch Inhibitor LY3039478[Online]. Indianapolis(IN): Lilly USA, LLC c2017 [cited 2018 Mar 17]. Available from URL: http://www.lillyoncologypipeline.com/molecule/notch-inhibitor/trials

relapsed/refractory non-Hodgkin lymphoma and acute lymphoblastic leukaemia, which was agreed by the PDCO in 2011. Until November 2017 no studies had been initiated in paediatric ALL although studies in other conditions (CLL and solid tumours) are registered in the EU clinical trial register.

Alisertib is the only small molecule being investigated as monotherapy. Alisertib (MLN8237) is classified as an orally active aurora kinase inhibitor (Liewer & Huddleston, 2018). Preclinical studies have shown that alisertib induces cell-cycle arrest and apoptosis (Ren et al, 2016). Alisertib is being investigated in NCT01154816, a multi arm clinical trial that aims to investigate the safety and efficacy of alisertib monotherapy in treating young patients (aged between 1 and 21 years) with relapsed or refractory solid tumours or leukaemia including ALL.

Two biologicals and three antibody drug conjugates are proposed as second line monotherapy in r/r Ph- ALL (Table 3-19). Blinatumomab, a bispecific monoclonal antibody that enables CD3-positive T cells to recognise and eliminate CD19-positive ALL blasts (Elias et al, 2017; Kantarjian et al, 2017), that is authorised in the EU and the US and is marketed by Amgen as Blincyto. In the EU, Blincyto is authorised for adult patients with B-ALL while in the US, it was also authorised for paediatric patients with B-ALL in addition to adult patients. In the EU, blinatumomab is being extensively studied in 4 phase II and phase III paediatric trials, where blinatumomab is being compared to conventional chemotherapy during the consolidation treatment phase in relapsed HR B-ALL.

Epratuzumab is the second biological being investigated for patients with r/r B-ALL. Epratuzumab is a monoclonal antibody that targets the CD22 surface antigen (Clowse et al, 2017). IntReALL-SR-2010 (EudraCT 2012-000793-30) is investigating if the

addition of epratuzumab after induction therapy improves outcome of standard risk (SR) relapsed precursor B-cell or T-cell ALL. Outside of ALL, Epratuzumab is being studied by UCB 46 for the treatment of systemic lupus erythematosus.

Three drug conjugates are currently being studied for children r/r Ph- ALL. Inotuzumab ozogamicin is an antibody-drug conjugate composed of an anti-CD22 mAb and a derivative of calicheamicin (Ricart, 2011). Inotuzumab ozogamicin is authorised in the EU as Besponsa and is indicated in adult patients with CD22-positive B-cell precursor ALL[47]. In trial NCT02981628 (AALL1621), the Children's Oncology Group is investigating inotuzumab ozogamicin monotherapy to treat younger patients (1 to 21 years) with r/r CD22 Positive B-ALL.

Moxetumomab pasudotox is a recombinant anti-CD22 immunotoxin composed of a fragment of an anti-CD22 monoclonal antibody fused to a fragment of *Pseudomonas* exotoxin A (Kreitman & Pastan, 2011; Wayne et al, 2017). Moxetumomab pasudotox was investigated in paediatric patients with r/r B-ALL or lymphoblastic lymphoma of B-cell origin in a multicentre, single-arm study (EudraCT 2012-003101-10). The company behind moxetumomab pasudotox is AstraZeneca and although a trial in paediatric B-ALL was carried out, the company is currently pursuing an indication in adult patients with hairy cell leukaemia (HCL)[48].

Coltuximab ravtansine is an antibody-drug conjugate composed of an anti-CD19 and a maytansine derivative (Hong et al, 2015). Coltuximab ravtansine was investigated as a

[46] UCB (Union Chimique Belge). Clinical Study Information – Epratuzumab [Online]. Brussels (BE): UCB S.A., Belgium; c2007 – 2018 [updated 2017 Mar 17; cited 2018 April 25]. Avialable from URL: https://www.ucb.com/our-science/Our-clinical-studies/epratuzumab

[47] European Medicines Agency. Product Information for Besponsa -EMEA/H/C/004119 -N/0002 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2018 Feb 1; cited 2018 Mar 25]. Available from URL: http://www.ema.europa.eu/ema

[48] AstraZeneca. US FDA accepts Biologics License Application for moxetumomab pasudotox in hairy cell leukaemia [Online]. Cambridge (UK): AstraZeneca plc; c2018 [updated 2018 April 03; cited 2018 April 27]. Available from URL https://www.astrazeneca.com/media-centre/press-releases/2018/us-fda-accepts-biologics-license-application-for-moxetumomab-pasudotox-in-hairy-cell-leukaemia-03042018.html

single agent for r/r ALL of B cell origin (including Burkitt's lymphoma) in trial EudraCT 2012-002961-36 sponsored by Sanofi-Aventis. In 2015, ImmunoGen acquired the rights to the product and was studying it in r/r diffuse large B-cell lymphoma (DLBCL)[49]

Two ATMPs, tisagenlecleucel and KTE-C19, are currently in development to treat children with r/r Ph- ALL in the EU. The most promising ATMP for paediatric ALL is tisagenlecleucel, an anti-CD19 chimeric antigen receptor (CAR) T-cell therapy (Maude et al, 2018) which was developed by Novartis for the EU and US markets. Tisagenlecleucel was authorised by the FDA in August of 2017 for the treatment of patients up to 25 years of age with B-cell precursor ALL that is refractory or in second or greater relapse and is marketed as Kymriah[50]. Novartis has submitted a marketing authorisation application to the EMA in November 2017[51]. Tisagenlecleucel as monotherapy for patients with r/r B-ALL has been studied in 5 phase II and phase III studies.

KTE-C19 is another example of CAR T-cell therapy that could potentially enter the market to treat children with ALL. The active substance of KTE-C19 is autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor and is being developed by Kite Pharma EU B.V. The company applied for a PIP with EMA and a single trial was agreed to by the PDCO in September 2017. The trial known as ZUMA-4 is registered in the EU clinical trial register as EudraCT

[49] ImmunoGen. Clinical pipeline coltuximab-ravtansine [Online]. Waltham(MA): ImmunoGen Inc; c2018 [cited 2017 May 6]. Avialable from URL: http://www.immunogen.com/pipeline/coltuximab-ravtansine

[50] Food and Drug Administration. Vaccines, Blood & Biologics -KYMRIAH (tisagenlecleucel) [Online]. Rockville (MD): U.S. Department of Health and Human Services; c2007 [cited 2018 Mar 17]. Available from URL: https://www.fda.gov/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/ucm573706.htm

[51] Novartis. Novartis reaches another regulatory milestone for CTL019 (tisagenlecleucel) with submission of its MAA to EMA for children, young adults with r/r B-cell ALL and adult patients with r/r DLBCL [Online]. Basel(CH): Novartis International AG; c2018 [Updated 2017 Nov 6: cited 2018 Mar 17]. Available from URL: https://www.novartis.com/news/media-releases/novartis-reaches-another-regulatory-milestone-ctl019-tisagenlecleucel-submission

2015-005010-30 and is a phase I/II multi-centre study evaluating KTE-C19 in paediatric and adolescent subjects with r/r B-ALL.

3.3.1.3 Prospective treatment protocol for bone marrow transplantation

Twelve prospective products were proposed for use in the HSCT procedure (Table 3-20). Two small molecules were proposed as part of multidrug conditioning regimens, 2 ATMPs were proposed as off-the-shelf donor substitutes in situations were no suitable donors are available and 8 products, one biological and 7 ATMPs were proposed as adjunctive therapies to HSCT.

Treosulfan and fludarabine were the two small molecules proposed as part of multidrug conditioning regimens. Treosulfan is an alkylating agent that is indicated for the palliative treatment of epithelial ovarian cancer although its use in treosulfan-based conditioning before hematopoietic stem cell transplants is well documented (Wachowiak et al, 2011; Danylesko et al, 2012). Treosulfan based regimens with or without TBI for HSCT in children are being investigated in 4 clinical studies including in a trial sponsored by Medac as part of an agreed PIP. In these trials investigators aim to investigate an alternative myeloablative regimen that takes advantage of treosulfan potent immunosuppressive characteristics and favourable toxicity profile (Danylesko et al, 2012).

Fludarabine is a purine analogue (Pettitt, 2003) indicated for B-cell chronic lymphocytic leukaemia (CLL). The use Fludarabine based preparative regimens in children as reduced-toxicity conditioning is being studied in ten trials.

Table 3-20: Products proposed for conditioning prior to HSCT, as adjunctive therapy and as off-the shelf donor substitutes.

Active Substance (Drug Class)	Drug Category	Trial Description	EudraCT Number or NCT Number
ATIR101 (Donor Lymphocyte Infusion)	ATMP	ATIR101 administered as an adjunctive immunotherapeutic on top of HSCT as adjunctive therapy to HSCT	EudraCT 2015-002821-20, EudraCT 2016-004672-2
BPX-501 with CaspaCIDe T cells (CAR T-cells)	ATMP	BPX -501 after mismatched, T depleted allo-transplantation in patients with haematological malignancies as adjunctive therapy to HSCT	EudraCT 2014-000584-41
CD19ζ chimeric antigen receptor gene-modified EBV-specific CTLs (CAR T-Cells)	ATMP	CD19 transduced EBV-CTL in CD19+ precursor B–ALL patients after undergoing allo-HSCT as adjunctive therapy to HSCT	EudraCT 2007-007612-29
CD25/71 allodepleted donor T cells (Donor Lymphocyte infusion)	ATMP	CD25/71 allodepleted donor T-cells to improve T-cell reconstitution as adjunctive therapy after allo-HSCT	EudraCT 2013-000872-14
Fludarabine (Purine analogue antimetabolite)	Small Molecule	Fludarabine in combination with other agents with or without TBI as conditioning prior to HSCT	EudraCT 2012-003032-22, NCT00448201, NCT01251575, NCT01527045, NCT01529827, NCT00914940, NCT01858740, NCT02220985, NCT00732316, NCT01028716
Mesenchymal stem cells (MSC)	ATMP	Co-transplantation of MSC as adjunctive therapy to HSCT	EudraCT 2008-005594-35, EudraCT 2009-011817-26
MM-TK donor lymphocytes (Donor Lymphocyte infusion)	ATMP	MM-TK donor lymphocytes vs standard strategy in HR ALL paediatric patients undergoing HSCT as adjunctive therapy to HSCT	EMEA-001370-PIP02-13
NiCord (Ex vivo expanded cell graft derived from umbilical cord stem cells)	ATMP	NiCord vs unmanipulated umbilical cord blood for patients with haematological malignancies in cases where no suitable donor is available	EudraCT 2014-000074-19, EudraCT 2015-004813-26, EudraCT 2016-000704-28
Off-the-Shelf Expanded Cord Blood Cells	ATMP	IV ex vivo-expanded cord blood progenitor cells given after unmanipulated UCB as adjunctive therapy to HSCT	NCT01175785
Rituximab (Anti-CD20 monoclonal antibody)	Biological	Pre- and post-transplant rituximab for patient with r/r CD20+ B-ALL as adjunctive therapy to HSCT	NCT00867529
StemEx - Carlecortemcel-L (Graft of stem/progenitor cells isolated and expanded from umbilical cord blood)	ATMP	Transplantation of StemEx in patients with HR haematological malignancies in cases where no suitable donor is available	EudraCT 2006-005159-14
Treosulfan (Alkyl sulfonate)	Small Molecule	Treosulfan in combination with other agents with or without TBI as conditioning prior to HSCT	EudraCT 2011-001534-42, EudraCT 2013-003604-39, NCT00796068, NCT00860574

Two ATMPs were proposed as off the shelf donor substitutes. Both products contain allogenic *ex vivo* expanded umbilical cord blood. StemEx (USAN carlecortemcel-l) was the earliest of the two products and was investigated by Teva Pharmaceutical Industries and Gamida-Cell in a joint venture project. A single multi-centre, multi-national, historical cohort-controlled phase II/III trail (EudraCT Number: 2006-005159-14) investigated StemEx in 101 patients with hematologic malignancies between October 2007 to 20 February 2012. NiCord is the second product based on an *ex vivo* expanded cell graft derived from umbilical cord stem cells and is being investigated by Gamida Cell in 3 clinical trials. Investigators are comparing the safety and efficacy of NiCord with unmanipulated cord blood unit transplantation in patients with haematological malignancies following conditioning therapy. Through such products Gamida Cell aims to address the limited availability of donors for patients with high-risk blood cancers in situations of an urgent allogeneic stem cell transplant,

Eight products are being investigated as adjunctive therapy to HSCT (Table 3-20). Two out of 8 products (1 biological and 1 ATMP) are being studied as adjuncts to be administered both before and after transplantation while 6 products (all ATMPs) are being studied for administration after or during transplantation only.

Rituximab administered pre- and post-translation is the single biological being investigated for HSCT. The trial is an open label, single arm study sponsored by the Fred Hutchinson Cancer Research Centre in collaboration with the National Cancer Institute (NCI) and aims to investigate if patients with r/r CD20 positive B-cell malignancies who receive IV rituximab, three days pre-transplant and post-tranplant on days, 10, 24, and 38 will experience improved outcome

The other products (n=7) being investigated as adjuvants to HSCT were ATIMPs, 2 were gene therapy medical product, 4 were somatic cell therapy medicinal products and 1 was both gene and somatic cell therapy medicinal product.

MM-TK (MolMED-Thymidine kinase) donor lymphocytes is a cell based adjunctive treatment for HSCT that involves infusion of cells genetically modified *ex vivo* to express a suicide gene that allows rapid control and abrogation of the possible onset of GvHD reaction[52]. MM-TK donor lymphocytes is approved for adult patients with high risk haematological malignancies undergoing HSCT in the EU as Zalmoxis[53]. The active substance in MM-TK is formally known as herpes simplex 1 virus thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes. Studies in children have not been initiated, although according to the agreed PIP EMEA-001370-PIP02-13, two clinical trials are planned. The planned trials are in paediatric patients who are candidates for HSCT and specifically in children with ALL.

BPX-501 and rimiducid is a combination advanced therapy medicinal product developed by Bellicum Pharma Ltd as an adjuvant to HSCT in paediatric ALL[54]. BPX-501 (recommended International Nonproprietary Name (INN) rivogenlecleucel[55]) is expanded donor-derived allogenic T cells transduced with the retroviral vector expressing the transgenes for inducible caspase9 and the truncated CD19 selectable marker and rimiducid is a lipid-permeable tacrolimus analogue with homodimerizing

[52]Molmed. Pipeline - TK [Online]. Milan(IT): MolMed S.p.A; c2018 [cited 2018 May 27]. Available from URL: http://www.molmed.com/node/17

[53] European Medicines Agency. Product Information for Zalmoxis -EMEA/H/C/002801 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2016 Sep 5; cited 2018 Mar 25]. Available from URL: http://www.ema.europa.eu/ema

[54] Bellicum Pharmaceuticals. BPX-501: Encouraging Results to Date in Haploidentical Hematopoietic Stem Cell Transplantation [Online]. Houston (TX): Bellicum Pharmaceuticals, Inc; c2018 [cited 2018 May 27]. Available from URL: http://www.bellicum.com/product-candidates/bpx-501/

[55] World Health organization. Recommended International Nonproprietary Names: List 79. WHO Drug Information 2018:32;89-186. Available from URL: http://www.who.int/medicines/publications/druginformation/en/

activity[56]. The BPX-501 component of the combination product aims to enhance immune reconstitution and retain the graft-versus-leukemia (GvL) effect of the transplanted allograft and infusion rimiducid can reduce acute GvHD in patients who develop severe GvHD. BPX-501 and rimiducid is currently being studied in an open-label, non-randomised, externally-controlled, single arm trial (EudraCT 2014-000584-41). An additional observational study (Study C-004) is planned for BPX-501 and rimiducid as per agreed PIP EMEA-001869-PIP01-15.

ATIR101 is a T-lymphocyte enriched leukocyte preparation depleted *ex vivo* of host alloreactive T-cells through using proprietary photodepletion technology developed by Kiadis Pharma[57]. ATIR101 is currently being investigated for use in adults in two trials, trial EudraCT 2015-002821-20 (CR-AIR-008) and EudraCT 2016-004672-21 (CR-AIR-009). An additional paediatric trial is planned according to the agreed PIP EMEA-001980-PIP01-16.

Academia is sponsoring 4 out of the 7 ATMP based studies in HSCT. Co-transplantation of mesenchymal stem cells (MSC) in patients undergoing HSCT is being studied in 2 trials in 2 university hospitals. Trial EudraCT 2009-011817-26 is being carried out in Universitair Ziekenhuis Brussels and trial EudraCT 2008-005594-35 in CHU Sart-Tilman in Belgium. In both trials the efficacy of MSC to prevent rejection, decrease graft-versus-host disease and enhancing engraftment is being investigated. University College London (UCL) is a public research university currently studying 2 CAR-T cells-based therapies in children with high risk ALL undergoing HSCT. In trial

[56] National Cancer Institute. Rimiducid (Code C82412) [Online]. Bethesda (MD): National Cancer Institute and NCI Enterprise Vocabulary Services; c2018 [updated 2018 April 12; cited 2018 May 27]. Available from URL: https://ncit.nci.nih.gov/ncitbrowser/ConceptReport.jsp?dictionary=NCI_Thesaurus&ns=NCI_Thesaurus&code=C82412

[57] Kiadis Pharma. Products ATIR101 [Online]. Amsterdam(NL): Kiadis Pharma; c2018 [cited 2018 May 27]. Avialable from URL: http://www.kiadis.com/product/atir101/

EudraCT 2007-007612-29, UCL is investigating the feasibility, safety and biological effect of a gene therapy ATIMP, CD19ζ chimeric receptor transduced donor-derived Epstein-Barr virus (EBV)-specific cytotoxic T-lymphocytes (EBV-CTL) in patients with high risk or relapsed B -ALL after HSCT. In trial EudraCT 2013-000872-14, UCL is studying a somatic cell therapy ATMP, CD25/71 allodepleted donor T cells. The aim of EudraCT 2013-000872-14 is to determine whether adoptive immunotherapy with CD25/71 allodepleted donor T-cells can be safely used to improve T-cell reconstitution after unrelated donor stem cell transplant

The Fred Hutchinson Cancer Research Centre is also investigating the safety and efficacy of *ex vivo* expanded cord blood progenitor cells as an adjuvant to unmanipulated umbilical cord blood transplantation in patients with haematologic malignancies in trial NCT01175785. The hypothesis of investigators is that the addition of expanded progenitor cells may decrease the time of leukocyte recovery after transplantation.

3.3.1.4 Prospective First line Philadelphia positive ALL

One product, dasatinib, was identified as a specific treatment for *de novo* Philadelphia chromosome positive paediatric ALL. Other investigational medicinal products could be incorporated into the Ph+ chemotherapy backbone based on studies in Ph- ALL patients. These products have been discussed as part of the First line Philadelphia chromosome negative ALL protocol in Section 3.3.1.1.

The only product in development for children with Ph+ ALL was dasatinib, a small molecule second generation tyrosine kinase inhibitor (Liu-Dumlao et al, 2012; Yu et al, 2017). Dasatinib was first authorised in the EU in November 2006 under the trade name

Sprycel[58]. Currently dasatinib is authorised exclusively in adults for newly diagnosed chronic, accelerated and blast phase CML with resistance or intolerance to prior therapy including imatinib mesylate and for Ph+ ALL with resistance or intolerance to prior therapy[52].

Dasatinib and combination chemotherapy for newly diagnosed patients with Ph+ ALL is currently being investigated in 6 trials. Trials sponsors include industry (Bristol-Myers Squibb in EudraCT 2011-001123-20) and expert groups such as the Children's Oncology Group in COG protocol AALL0622 (registered trials EudraCT 2010-022946-25 and NCT00720109) and National Cancer Institute (NCI) in NCT02883049.

3.3.1.5 Prospective Second line Philadelphia positive ALL

Two small molecules, dasatinib and ponatinib, were proposed as second line agents for Philadelphia positive ALL. Both products were TKIs and were described in paediatric investigation plans.

Dasatinib will be studied in r/r Ph+ acute lymphoblastic leukaemia to fulfil PIP number EMEA-000567-PIP01-09-M04. The second TKI to be studied for r/r Ph+ ALL is Ponatinib. The target indication agreed by the PDCO in PIP number EMEA-001186-PIP01-11-M01 is *"For the treatment of the paediatric population with Ph+ ALL who are resistant or intolerant to prior TKI therapy".* Ponatinib is marketed by Incyte

[58]European Medicines Agency. Product Information for Sprycel -EMEA/H/C/000709 -II/0055 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2017 Jul 7; cited 2018 Mar 28]. Available from URL: http://www.ema.europa.eu/ema

Biosciences UK Ltd in the EU as Iclusig and is authorised for CML or Ph+ ALL in adult patients who are resistant or intolerant to other TKIs[59].

In the proposed second line protocol for Ph+ ALL other strategies that could be utilised after multiple TKI failure are presented. Three products, inotuzumab ozomycin, coltuximab ravtansine and tisagenlecleucel, are being studied for Ph+ ALL in second relapse or greater as monotherapy.

3.3.2 Prospective Products in Phase I and Phase I/II Trials

Products described in ongoing and completed phase I and phase I/II trials initiated after November 2007 are presented in Appendix 5. Drug category analysis showed that 27 were small molecules including 3 novel formulations, 13 were ATMPs, 2 were biologicals and 2 were antibody drug conjugates.

3.4 Clinical Development Programs

The following section briefly describes the CDPs for CAPs and prospective products described in PIPs. For a more detailed outline of CDPs for CAPs refer to Appendix 4

3.4.1 CDPs of centrally authorised products

Clinical development programs are presented according to the legal basis of application. Four different legal bases were observed in CAP applications for paediatric ALL. These were; (i) article 8(3) of Directive 2001/83/EC (full application), (ii) article 10(3) of Directive 2001/83/EC (hybrid application), (iii) article 10a of Directive 2001/83/EC

[59] European Medicines Agency. Product Information for Iclusig -EMEA/H/C/002695 -R/0042 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2017 Jul 7; cited 2018 Mar 28]. Available from URL: http://www.ema.europa.eu/ema

(well-established use application) and (iv) Article 14 (8) of the Regulation (EC) No 726/2004 (marketing authorisation under exceptional circumstance).

3.4.1.1 Well-established use (WEU) applications

Two products, Busilvex and Tepadina, were identified to have been approved through the legal basis of WEU. Busilvex (busulfan solution for infusion) was submitted as a so-called "bibliographical application", in accordance with article 4.8 (a) ii of Directive 65/65/EEC. Article 4.8 (a) ii states that a list of published references relating to pharmacological tests, toxicological tests and clinical trials may be substituted for the relevant test results in the case of a new proprietary product, with a combination of active constituents identical to that of a known proprietary product with an established use[60]. The European Commission granted the initial marketing authorisation for Busilvex (IV busulfan) on 9 July 2003.

Prior to the authorisation of Busilvex, only low dose (2mg) tablets of busulfan were available in the EU. The company supplemented literature-based data and PK and safety and efficacy studies. The granted adult indication was as follows *"Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option"*. The paediatric indication was granted on 31st of October 2005 through a type II variation application. The wording for the paediatric indications is as follows *"Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients"*.

[60]The European Parliament and the Council of the European Union. Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by Law, Regulation or Administrative Action relating to proprietary medicinal products. OJ. 1965; P022: 20-24

The CDP for Busilvex in adults consisted of two PK studies and two phase II studies. Two supportive studies were also submitted. The CDP for Busilvex in children consisted of two phase II studies. The total adult population exposed to Busilvex was 154 affected patients while the total paediatric population exposed was 79 affected patients. Patients recruited were candidates for allogenic HSCT and had different underlying malignant or non-malignant conditions. Patients that were candidates for autologous HSCT were also considered.

Endpoints used in PK studies were dose-normalised ratio of IV, AUC at first dose, versus oral AUC at steady-state and target AUC range. Safety and efficacy endpoints were divided into short term and long-term endpoints. The short-term endpoints used for both adult and children were myeloablation and engraftment. The long-term endpoints were disease-free survival (DFS) or event free survival, relapse, overall survival and transplant-related mortality

Tepadina was submitted as a well-established use application according to Article 10(a) of Directive 2001/83/EC. The European Commission granted a marketing authorisation for Tepadina on 15th March 2010. A full bibliographical dossier containing published clinical studies performed in adult and paediatric patients was submitted. A total of 109 publications were submitted, that together studied thiotepa in 6,000 adults and 900 children with blood diseases or solid tumours. The studied leukemic population was 586 adults and 228 children presented in 14 published studies.

3.4.1.2 Hybrid Applications

Two products, Jylamvo (methotrexate oral solution) and Xaluprine (mercaptopurine oral suspension) were identified to have been approved through hybrid application. Hybrid applications are a type of marketing authorisation application defined under

article 10(3) of Directive 2001/83/EC. Companies apply for a marketing authorisation through a hybrid application when the definition of a generic medicinal product is not met and where the bioavailability studies cannot be used to demonstrate bioequivalence. In hybrid applications the results of appropriate pre-clinical tests and clinical trials are necessary since there are changes in the active substance(s), therapeutic indications, strength, pharmaceutical form or route of administration of the prospective generic product when compared to the reference medicinal product.

The European Commission granted a marketing authorisation for Jylamvo on 29 March 2017. The reference product was Methotrexat "Lederle" 2.5mg tablets (Pfizer Corporation Austria Ges.m.b.H). The CDP did not contain new clinical efficacy and safety data and was based on 2 BE studies involving 48 healthy adult volunteers. The primary PK endpoints were the maximum observed plasma concentration (C_{max}) and the area under the plasma concentration versus time curve (AUC). Several secondary PK endpoints were also studied including the time to C_{max} (tmax), terminal elimination rate constant (λz) and apparent terminal elimination half-life (t½). The second BE study (MTX002) monitored patient safety variables including haematology, clinical chemistry, urinalysis and adverse events (AEs).

The European Commission granted a marketing authorisation for Xaluprine on 9th March 2012. The reference product was Puri-Nethol 50 mg Tablets (GlaxoSmithKline UK). No new clinical efficacy and safety data was submitted, and the CDP was based on one BE study that aimed to evaluate the PK characteristics and bioavailability of the test formulation with the reference product. The BE study submitted used a randomised, two-treatment, two-period, two-sequence single-dose crossover study and involved 60 healthy adult males with a mean age of 23. The company justified the choice of adults over children since the reference product is used in adult and children without any

dosing difference and the actual dose is based on body surface area. Three primary PK endpoints, Cmax, AUC_{0-t} and $AUC_{0\ -infinity}$ were used.

3.4.1.3 Complete and Independent Applications

Three products, Glivec, Oncaspar and Spectrila, were identified to have been granted a marketing authorisation through complete and independent applications as defined in article 8 of Directive 2001/83/EC. Complete and independent applications (also referred to as full applications) need to contain the results of pharmaceutical tests such as physico-chemical, biological or microbiological tests, pre-clinical pharmacological and toxicological tests and clinical trials.

Glivec (imatinib) was first authorised in November 2001 as second line treatment for chronic myeloid leukaemia in adults. An extension of induction for Glivec with the following wording *"Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy and of adult patients with relapsed or refractory Ph+ ALL as monotherapy"* was granted in September 2006 through a type II variation (Glivec-H-C-406-II-0031). An extension of the indication of Glivec for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy was granted in June 2013 through another type II variation (Glivec-H-406-II-80)[61]. The legal basis used for the extension of the indication of Glivec was the 'prior approval' procedure for major variations of type II in accordance with article 16 of Commission Regulation (EC) No 1234/2008.

[61] European Medicines Agency. Glivec - Procedural steps taken and scientific information after the authorisation [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2017 Nov 6; cited 2018 Mar 28]. Available from URL: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Procedural_steps_taken_and_scientific_information_after_authorisation/human/000406/WC500022206.pdf

The adult ALL indication of Glivec was based on 1 controlled and 9 uncontrolled open-label clinical trials that in total recruited 758 patients. Recruited patients included 443 patients with relapsed/refractory Ph+ ALL and 315 patients with *de novo* Ph+ ALL. Dose finding studies were not performed in patients with ALL since the dose was established in previous trials in patients with CML. The majority of studies were phase II trials (n = 9) and one was a phase I trial. Studies submitted evaluated imatinib monotherapy as induction therapy, in combination with corticosteroid only and in combination chemotherapy. Various efficacy endpoints were used, including complete haematological response, cytogenetic response, minimal residual disease (MRD), remission duration and relapse rate, disease free survival (DFS), event free survival (EFS) and overall survival (OS).

The CDP for Glivec in paediatric patients consisted of a physiologically-based pharmacokinetic (PBPK) model based on 4 studies (2 phase I dose finding studies, 1 phase II study and one PK study), one pivotal phase II trial and one supportive phase II trial. In total, 220 paediatric patients with Ph+ ALL were exposed to imatinib during the clinical trials in children submitted in support of the indication extension for Glivec. The primary efficacy endpoints were EFS and DFS and the secondary endpoints were OS, comparison of safety between imatinib and chemotherapy compared to chemotherapy alone, molecular response as a surrogate for DFS, exposure-response of imatinib and MRD.

Oncaspar (pegaspargase) was authorised by the European Commission on the 14th January 2016. The granted EU indication is *"Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients"*. The company submitted two sets of efficacy data in support of Oncaspar indication, (i) trials for *de novo* ALL

(so called first line indication) and (ii) trials for relapsed ALL patients (second line indication). Four pivotal clinical trials and two additional studies were submitted for *de novo* ALL and 8 studies were submitted in support of Oncaspar in r/r ALL. In this project only, studies in support of Oncaspar for *de novo* ALL were reviewed.

CCG-1961 was the main study in support of Oncaspar. CCG-1961 was a multicentre prospective randomized, open label phase III trial that ran from September 1996 till May 2002 and was submitted by the company as 4 bibliographic references. The other pivotal studies (CCG-1962, DFCI-87-001, DFCI-91-01) were phase II (n=1) and phase III (n=2) multicentre randomised studies to investigate the safety and efficacy of Oncaspar. Additional studies, DFCI-05-001 and AALL07P4, also supported the efficacy of Oncaspar in newly diagnosed ALL patients. Across the 6 studies submitted, a total of 687 patients were treated with Oncaspar. The main efficacy endpoint used across all efficacy trials was EFS, were data taken at 3 years, 5 years and 7 years was presented. Other endpoints investigated were OS, CR and leukemic cell kill rate measure in peripheral blood and bone marrow. Health related quality of life (HR-QOL), focused on anxiety and pain, was investigated in study DFCI-05-001.

Spectrila (recombinant L-asparaginase produced in *E. coli***)** was authorised by the European Commission granted a marketing authorisation for Spectrila on the 14th January 2016. Five clinical trials were submitted in support of Spectrila; 1 pivotal phase III trial in newly diagnosed children with ALL, 2 phase II trials in newly diagnosed children with ALL including one trial in infants and 2 small PK studies in adults with relapsed haematological malignancies. In total 126 children with ALL were exposed to Spectrila in three trials. The primary PK endpoint was AUC 0-72h and additional secondary PK endpoints were C_{max}, T_{max}, terminal elimination rate constant and terminal elimination half-life. The primary efficacy endpoint in the pivotal trial was

complete ASN depletion. Additional efficacy endpoints measured were CR rate, MRD status and EFS.

3.4.1.4 Applications for marketing authorisation under exceptional circumstance

Two products, Atriance and Evoltra, were identified to have been approved under Exceptional circumstance. A marketing authorisation may be granted under exceptional circumstances when an applicant for marketing authorisation is unable to provide comprehensive data on the efficacy and safety under normal conditions. The EMA gives 3 reasons why comprehensive data could not be provided, (i) the indication is too rare, (ii) the present state of scientific knowledge needed to provide comprehensive information is insufficient or (iii); the collection of comprehensive information in support of the marketing authorisation would be unethical[62].

Atriance (nelarabine) was granted marketing authorisations on 22nd August 2007. The CDP in support of Atriance is based on 3 phase I trials and 2 phase II main trials. The company submitted 3 open-label, dose escalating safety and PK phase I studies to determine the MTD of nelarabine. The patient cohort studied in phase I trials (n = 3) consisted of adults (n = 128) and children (n = 40) affected by different haematological malignancies. The main studies were, (i) an open label, multicentre clinical trial in adults with r/r T-ALL/ LBL and a two-stage, open label, multicentre paediatric clinical trial in children with r/r T-ALL/ LBL. The number of patients recruited in both trials was 39 adults and 70 children. The same endpoints were used in the adult and paediatric study. The primary endpoints were response rate, measure as complete response (CR),

[62] European Medicines Agency and Committee for Medicinal Products for Human Use. Guideline on procedures for the granting of a marketing authorisation under exceptional circumstances, pursuant to article 14 (8) of Regulation (EC) No 726/2004 – EMEA/357981/2005 [Online]. London (UK): European Medicines Agency; c1995-2017 [updated 2005 Dec 16; cited 2018 Mar 28]. Available from URL: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500004883

partial response (PR) and CRh* (CR but incomplete haematological recovery). The secondary endpoints were duration of response, time to response and overall survival (OS).

Evoltra (clofarabine) was granted marketing authorisations on 29th May 2006. The CDP in support of Evoltra was based on two phase I PK studies, one in adults and one in children, and one phase II trial in young patients (<21 years old). The phase I trials submitted studied 51 adults with solid tumours or hematologic malignancies who failed standard therapy and 25 paediatric patients with relapsed or refractory acute leukaemia. The endpoints used were MTD and DLT. The main study submitted was non-randomized, open-label, single-arm in 61 patients below 21 years old. The primary endpoints investigated were CR, complete remission in the absence of total platelet recovery (CRp) and PR, while the secondary endpoints used were duration of response, time to response and overall survival.

3.4.2 CDPs of prospective products described in PIPs

Clinical, physiologically based pharmacokinetic (PBPK) modelling based studies and other studies to be carried out in children with ALL as agreed in PIPs are summarised in Table 3-21. The table format was adopted from Rose & Walson, 2015. The PDCO agreed to 34 trials across 13 PIPs. The number of trials per PIP ranged from 1 to 5 trials, with an average of 2.6 trials. Most of the agreed trials were open label at 31 out of 34 trials. Other distinctive trial features were controlled trials observed in 9 out of 31 trials, randomised assignment observed in 7 trials and single arm trials observed in 4 trials. The PDCO agreed to physiologically based pharmacokinetic model for one PIP (EMEA-000530- PIP02-11) and to a literature-based study for treosulfan, where the company has to analyse all data on the uses of treosulfan in the paediatric population.

Table 3-21: Summary of agreed PIPs for prospective product to treat ALL or product for conditioning/ adjunctive treatment in HSCT in children. Table format adopted from Rose K, Walson PD. The contributions of the European Medicines Agency and its paediatric committee to the fight against childhood leukaemia. Risk Manag Healthc Policy. 2015;8:185-205.

Active Substance & PIP number	Clinical, modelling and other studies agreed by the PDCO
Autologous T-cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 (CTL019). EMEA-001654-PIP01-14-M02	1. OL SA posology- finding study to evaluate S and F of administration of redirected autologous T-cells engineered to contain anti-CD19 attached to TCRzeta and 4-1BB signaling domains (CAR-19 cells) in patients from 1 year to <18 years (and adults) with a CT-resistant or CT- refractory CD19+ leukaemia or lymphoma. 2. OL SA, single- dose study to evaluate S and A of CTL019 in patients from 3 years to <18 years (and adults) with CD19+ B-cell ALL/CD19+ B- cell LL whose disease is refractory to a standard CT, relapsed after SCT or are otherwise ineligible for allogeneic SCT. 3. OL SA single- dose study to evaluate S and A of CTL019 from 3 to <18 years (and adults) with CD19+ B cell ALL whose disease is refractory to a standard CT, relapsed after SCR or are otherwise ineligible for allogeneic SCT. 4. OL two- cohort study to evaluate manufacturing and S of CTL019 in <3 years, weighing ≥ 6kg, with CD19+ B-cell ALL/CD19+ B-cell LL at high risk for relapse and at relapse or refractory stage.
Autologous T-cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3- zeta chimeric antigen receptor. EMEA-001862-PIP01-15	1. OL SA, 2- phase trial to evaluate S and A, of autologous T-cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor (KTE-C19) in children weighing ≥6kg with B-cell ALL (cohort 1) or with B-cell non- Hodgkin lymphoma (cohort 2) whose disease is refractory a standard CT, relapsed after SCT.
Navitoclax (ABT-263)) EMEA-000478-PIP01-08-M01	1. OL< S and PK study of APT-263 single- agent and combination therapy in paediatric patients from 28 days to <18 years of age with relapsed or refractory lymphoblastic leukaemia or LL. 2. R, controlled, S and A study of ABT-263 in combination with a chemotherapeutic backbone in patients with relapsed or refractory lymphoblastic leukaemia or LL.

Abbreviations: ALL, acute lymphoblastic leukaemia; PIP, paediatric investigation plan; OL, open-label; SA, single-arm; S, safety; F, feasibility; A, activity; CT, chemotherapy; SCT, stem cell transplantation; MC, multicentre; PK, pharmacokinetics; Ph+, Philadelphia chromosome-positive; CML, chronic myeloid leukaemia; E, efficacy; R, randomized; Pop, population; PD, pharmacodynamics; CAR, chimeric antigen receptor; LL, lymphoblastic lymphoma.

Table 3-21: Summary of agreed PIPs for prospective product to treat ALL or product for conditioning/ adjunctive treatment in HSCT in children. Table format adopted from Rose K, Walson PD. The contributions of the European Medicines Agency and its paediatric committee to the fight against childhood leukaemia. Risk Manag Healthc Policy. 2015;8:185-205.

Active Substance & PIP number	Clinical, modelling and other studies agreed by the PDCO
Blinatumomab EMEA-000574-PIP02-12-M01	1. MC, OL, multiple- dose, dose escalation trial to evaluate PK, PD, toxicity, S and anti-tumour activity of Blinatumomab in children from birth to <18 years of age with a relapse of B- precursor ALL involving the bone marrow or a refractory ALL and for whom no effective treatment is known, with an extension phase. 2. R, controlled, adaptively- designed, OL trial to evaluate the PK, S and E of Blinatumomab compared to multi- agent consolidation CT in children from 1 month to <18 years of age with a first, high- risk relapse of B- precursor ALL. 3. PK-PD analysis to inform the dose for clinical study 2
Cyclophosphamide EMEA-000530- PIP02-11	1. OL, R, MC, active- controlled trial to evaluate PK, toxicity and S of Cyclophosphamide soluble tablet compared with authorised Cyclophosphamide products in children from 6 months to <18 years of age with a malignant disease. 2. Physiology-based PK model with simulations, applicable to children from birth on.
Dasatinib EMEA-000567-PIP01-09-M04	1. OL MC dose escalation trial to evaluate PK and S of dasatinib in children from 2 years to <18 years (and in adults) with recurrent or refractory solid tumour or imatinib- resistant Ph+ leukaemia. 2. OL MC dose- escalation trial to evaluate PK an S of dasatinib in children from 1 year <18 years of age with Ph+ chronic myeloid leukaemia or acute leukaemia. 3. OL MC trial to evaluate PL, S and E of dasatinib in children from 1 year to <18 years of age with Ph+ chronic myeloid leukaemia of all phases (including treatment- naïve patients in chronic phase) or relapsed/ refractory Ph+ ALL. 4. OL MC trial evaluating S and tolerability of dasatinib in combination with multi- agent chemotherapy in children from 1 year to <18 years of age (and adults) with newly- diagnosed Ph+ ALL. 5. OL MC, historically- controlled trial to evaluate S and E of dasatinib plus chemotherapy compared to CT alone and compared to imatinib plus CT in children from 1 year to <18 years of age with newly diagnosed Ph+ ALL.

Abbreviations: ALL, acute lymphoblastic leukemia; PIP, paediatric investigation plan; OL, open-label; SA, single-arm; S, safety; F, feasibility; A, activity; CT, chemotherapy; SCT, stem cell transplantation; MC, multicentre; PK, pharmacokinetics; Ph+, Philadelphia chromosome-positive; CML, chronic myeloid leukemia; E, efficacy; R, randomized; Pop, population; PD, pharmacodynamics; CAR, chimeric antigen receptor; LL, lymphoblastic lymphoma.

Table 3-21: Summary of agreed PIPs for prospective product to treat ALL or product for conditioning/ adjunctive treatment in HSCT in children. Table format adopted from Rose K, Walson PD. The contributions of the European Medicines Agency and its paediatric committee to the fight against childhood leukaemia. Risk Manag Healthc Policy. 2015;8:185-205.

Active Substance & PIP number	Clinical, modelling and other studies agreed by the PDCO
L- asparaginase encapsulated in erythrocytes EMEA-000341-PIP02-09-M04	1. Double- blind, dose- comparative, R, repeat- dose, MC, active- controlled trial to evaluate PK, PD, S and immunogenicity of L-asparaginase encapsulated in erythrocytes in children from 1 year to <18 years (and in adults) with ALL. 2. OL, R, single dose, MC, active- controlled trial to evaluate PK, S, PD activity of L- asparaginase encapsulated in erythrocytes in children from 1 year to <18 years (and in adults) with first relapse of ALL, with and without asparaginase hypersensitivity. 3. OL, R, MC, active- controlled trial to evaluate S, PD equivalence/ comparative efficacy of L- asparaginase encapsulated in erythrocytes in children from birth to <18 years with newly- diagnosed ALL.
Momelotinib EMEA-001656-PIP01-14	1. Cohort-sequential, OL, non- controlled, single-agent dose-escalation trial to evaluate PK, S and anti- leukaemia activity of momelotinib in children from birth to <18 years (and young adults) with a relapsed or refractory ALL with a Janus kinase- activating mutation or with a CRLF2 overexpression for whom no effective treatment is available. 2. Cohort- sequential, OL, non- controlled dose- escalation trial to evaluate PK, S and anti- leukaemia activity of momelotinib in combination with a CT regiment in children from birth to <18 years of age (and young adults) with newly- diagnosed ALL with a JAK- activating mutation. 3. OL, controlled trial to evaluate S and E of momelotinib as add- on to a CT regimen in children from birth to <18 years (and young adults) with newly- diagnosed ALL with a JAK- activating mutation.
Ponatinib EMEA- 001186-PIP01-11-M01	1. OL, single- agent, dose- escalation, MC trial to investigate tolerability, S and A of ponatinib in the paediatric population from 1 year to <18 years of age with malignant disease for which no effective treatment is known and with an expansion cohort of the paediatric population with BCR-ABL translocation- positive ALL. 2. R, MC, dose- comparative, double- blind trial to investigate the S, A and E of ponatinib as add- on to standard therapy in the paediatric population from 1 year to <18 years of age with relapsed or refractory BCR-ABL translocation- positive ALL.

Abbreviations: ALL, acute lymphoblastic leukaemia; PIP, paediatric investigation plan; OL, open-label; SA, single-arm; S, safety; F, feasibility; A, activity; CT, chemotherapy; SCT, stem cell transplantation; MC, multicentre; PK, pharmacokinetics; Ph+, Philadelphia chromosome-positive; CML, chronic myeloid leukaemia; E, efficacy; R, randomized; Pop, population; PD, pharmacodynamics; CAR, chimeric antigen receptor; LL, lymphoblastic lymphoma.

Table 3-21: Summary of agreed PIPs for prospective product to treat ALL or product for conditioning/ adjunctive treatment in HSCT in children. Table format adopted from Rose K, Walson PD. The contributions of the European Medicines Agency and its paediatric committee to the fight against childhood leukaemia. Risk Manag Healthc Policy. 2015;8:185-205.

Active Substance & PIP number	Clinical, modelling and other studies agreed by the PDCO
Expanded donor- derived allogenic T-cells transduced with the retroviral vector expressing the transgenes for inducible caspase9 and the truncated CD19 selectable marker (BPX-501). EMEA- 001869-PIP01-15	1. OL, non- randomised, externally- controlled, SA trial with 2 phases to determine the highest tolerated dose (Phase 1) and to evaluate S and A (Phase 2) of BPX-501 and of rimiducid in children from birth to <18 years whose disease is deemed curable by HSCT but who do not have a matched donor (related or unrelated). (BP-004) (Same study as Study 1 in EMEA- 001870-PIP01-15) 2. OL, non- controlled trial to evaluate Opinion of the Paediatric Committee on the agreement of a PIP and on the refusal of a deferral EMA/PDCO/115488/2017 Page 5/13 PK and S of rimiducid in children from 2 months to <18 years with recurrent or MRD hematologic malignancies after prior allogeneic transplantation. (BP-1-008) 3. Observational study in children from birth <18 years whose disease is deemed curable by HSCT but who do not have a matched related donor but who have an alternative eligible MUD, to collect S and E data of MUD transplant in these patients with haematopoietic disorders, both malignant and non- malignant. (C-004)
Herpes simplex 1 virus thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes. EMEA-001370-PIP02-13	1. OL, non- randomized trial to evaluate the maximum tolerated dose and the A of MM-TK cells administered in paediatric patients from birth to <18 years who are candidates for haploidentical HSCT. (TK009 IPR/27.A) 2. R, active- controlled, OL, MC study to evaluate activity of MM-TK donor lymphocytes compared to standard strategy in high risk acute leukaemia paediatric patients undergoing haploidentical HSCT (TK010 IPR/28.A)
T- lymphocytes enriched leukocyte preparation depleted ex vivo of host-alloreactive T-cells using photodynamic treatment (ATIR101) EMEA-001980-PIP01-16	1. MC, OL, R controlled trial with dose- finding run0 in to evaluate the toxicity, S and E of donor T- lymphocytes depleted ex vivo of host alloreactive T cells using photodynamic treatment (ATIR101) administered after receipt of a T- cell depleted HSCT from a related, haploidentical donor compared with a HSCT from an umbilical cord blood unit of an unrelated donor.
Treosulfan EMEA-000883-PIP01-10-MO4	1. R, active- controlled, OL, MC to evaluate PK, A and S of treosulfan compared with busulfan in children with a non- malignant disease. 2. MC, non- controlled, OL trial to evaluate PK, A and S of treosulfan in children with a malignant disease. 3. Study to analyse of all data on paediatric uses of treosulfan.

Abbreviations: ALL, acute lymphoblastic leukaemia; PIP, paediatric investigation plan; OL, open-label; SA, single-arm; S, safety; F, feasibility; A, activity; CT, chemotherapy; SCT, stem cell transplantation; MC, multicentre; PK, pharmacokinetics; Ph+, Philadelphia chromosome-positive; CML, chronic myeloid leukaemia; E, efficacy; R, randomized; Pop, population; PD, pharmacodynamics; CAR, chimeric antigen receptor; LL, lymphoblastic lymphoma

3.5 CDP comparisons

In this section, 3 CDPs comparisons are presented (Table 3-22 to Table 3-24). A summary of CDP comparisons and rationale for selection is compiled in Method section, Table 2.2. Comparisons are based on phase II and phase III trials for adult and paediatric ALL as discussed in EPARs and Paediatric Investigation Plans or registered in the EU clinical trial register and clinicaltrials.gov.

Four asparaginase depleting agents were compared (Table 3 22). Two were authorised products and 2 were prospective products. Oncaspar is a new pegylated formulation of asparaginase authorised in January 2016. Spectrila is a recombinant version of *E. coli* derived asparaginase that is manufactured to be identical to Asparaginase Medac, also authorised in January 2016. The 2 prospective asparaginase products are GRASPA, a propriety formulation of L-asparaginase encapsulated in erythrocytes and Calaspargase pegol, which another pegylated form of asparaginase, similar to Oncaspar.

Out of the four asparaginases analysed Oncaspar had the most comprehensive CDP, which consisted of 1 phase II trial, three phase III trials and 2 supportive studies that in total exposed 687 *de novo* ALL patients to Oncaspar. An additional 8 trials that recruited 293 adults and children with relapsed or refractory haematological malignancies were presented by the company. Safety data from study CCG-1991 that monitored the safety of pegaspargase in 2957 patients was also presented. Specrila and Graspa had similar CDPs, both products had 2 phase II trials and a single-phase III trial. Calaspargase pegol was observed to have the lowest number of trials, 1 phase II and 1 pilot PK/PD trial. Calaspargase pegol is listed as part of the treatment regimen in two additional trials registered in clinicaltrials.gov that are studying biomarkers to classify young patients with ALL and not the efficacy of Calaspargase pegol.

Table 3-22: Comparison of authorised and prospective asparaginase depleting agents for paediatric acute lymphoblastic leukaemia

	Oncaspar (Baxalta) Pegaspargase Initial MA granted in Jan 2016 as part of multiagent CT for children and adults with ALL		**Spectrila (Medac)** Asparaginase (Produced in Escherichia coli cells by recombinant DNA technology) Initial MA granted in Jan 2016 as part of multiagent CT for children and adults with ALL		**Graspa (Erytech Pharma AS)** Eryaspase (L-asparaginase encapsulated in red blood cells) Development Phase II/III		**Calaspargase pegol (Baxalta)** Alternatives Names: SHP-663, SC-PEG or EZN-2285 Development Phase II	
	Healthy Volunteers	**Affected patients**	**Healthy Volunteers**	**Affected patients**	**Healthy Volunteers**	**Affected patients**	**Healthy Volunteers**	**Affected patients**
Phase II	**N/A**	**Study CCG-1962** • MC, R, S, E & PK study • Children with newly diagnosed, SR-ALL. Oncaspar group N = 59/118 • EFS, Anti-asparaginase antibody ratio	**N/A**	**Study MC-ASP.4/ALL** • Single centre, double blind, controlled, parallel assignment, PK/PD, E & S study • Children with newly diagnosed ALL. Spectrila group N = 16/32 • AUC 0-72h, PK endpoint, AEs **Study MC-ASP.6/INF** • Uncontrolled MC, PD, E & S, study • Infants with previously untreated *de novo* ALL. N =12 • Number of pts with hypersensitivity reactions,	**N/A**	**Study GRASPALL2009-06** • MC, OL, R, E & S study • Adults and children with r/r ALL. N =80 • Asparagine depletion, Incidence of allergic reaction **Study NOR-GRASPALL-2016 (*Ongoing*)** • MC, Single arm, PK/PD & S study • Children and adults with hypersensitivity to peg-asparaginase. N =30 • Safety and Tolerability, PK parameter PD profile, Immunogenicity (anti-asparaginase antibodies) and incidence of hypersensitivity	**N/A**	**Study NCT01574274 (*Ongoing*)** • OL, R, 2 arm parallel assignment Study of IV Calaspargase Pegol vs IV Oncaspar • Previously untreated patients (1 – 21 years) will ALL or Lymphoblastic Lymphoma. Recruited N = 240 • Asparaginase-related toxicity, Asparaginase PK
Phase III	**N/A**	**Study CCG-1961** • MC, OL, partially R, E study with 2 x 2 factorial design • Children with newly diagnosed, HR-ALL. Oncaspar group N = 163/2077 • EFS, OS **Study DFCI-87-001** • MC, OL, R in vitro/vivo 3 arm sub-study • Children with newly diagnosed ALL. to Oncaspar group: 84/251 • EFS, In vitro mean total cell kill rate **Study DFCI-91- 01** • MC, OL, R, Controlled E & S study with parallel assignment • Children with newly diagnosed ALL. Oncaspar group N =106/325 • 5-y EFS	**N/A**	**Study MC-ASP.5/ALL** • MC, R, Active-controlled, double blind, parallel assignment, non-inferiority study • Children with *de novo* ALL. Spectrila group N = 98/199 • Complete ASN depletion	**N/A**	**Planned Study as per EMEA-000341-PIP02-09-M04** • OL, R, MC, active- controlled trial to evaluate S, PD equivalence/ comparative efficacy of L- asparaginase encapsulated in erythrocytes • Children from birth to <18 years with newly- diagnosed ALL.	**N/A**	**N/A**
Supportive Studies	**N/A**	**Study DFCI-05-001 -** OL, R, phase III study. N = 232 children *de novo* ALL. **Study AALL07P4 -** PK/PD Pilot Study. HR-ALL patients (1 – 30 years) with 43 patients receiving Oncaspar		**Study MC-ASP.1/ALL-**OL, uncontrolled phase II study, N= 2 Adult with r/r ALL				**Study AALL07P4** PK/PD Pilot Study. HR-ALL patients (1 – 30 years) with 111 patients receiving Calaspargase pegol
	Total Exposed = 687		**Total Exposed = 118**		**Total Exposed (Until Nov 2017) = 120**		**Total Exposed (Until Nov 2017 - Estimated) = 231**	

Abbreviations: ASN, asparagine; ALL, acute lymphoblastic leukemia; PIP, pediatric investigation plan; OL, open-label; SA, single-arm; S, safety; F, feasibility; A, activity; CT, chemotherapy; SCT, stem cell transplantation; SR, standard risk; MC, multicenter; PK, pharmacokinetics; Ph+, Philadelphia chromosome-positive; CML, chronic myeloid leukemia; E, efficacy; R, randomized; Pop, population; PD, pharmacodynamics; CAR, chimeric antigen receptor; LL, lymphoblastic lymphoma; MA, Marketing Authorisation

All asparaginase depleting agents had or have planned randomised controlled trials comparing the test product to other asparaginase depleting agents.

Three authorised TKI products were compared (Table 3-23). Glivec sought a staggered approach to an ALL indication where initial MA was granted for adults with CML, then through successive post authorisation variations the company sought an indication in ALL, first in adults and then in children. The other two products, Sprycel and Iclusig, were granted an indication for CML and Ph+ ALL in adults simultaneously. Both products are carrying out trials in children in pursuit of an indication in children with Ph+ ALL.

The CML indication of Glivec was based on 3 open-label, non-controlled phase II trials. One of the CML trials (Study 0109) also recruited patients with Ph+ ALL and was presented again, together with 8 other phase II trials and 1 phase I trial, in support of the Ph+ ALL indication in adults. The paediatric indication of Glivec in newly diagnosed Ph+ ALL was based on 2 phase II trials and a PBPK model that utilised data from 4 PK studies.

The initial authorisation of Sprycel for CML and Ph+ ALL in 2006, was based on 6 studies, 1 phase I and 5 pivotal phase II trials. All recruited subjects were intolerant or resistant to imatinib and most were diagnosed with chronic, accelerated and blast phase CML and only one trial (Study CA180015) recruited patients with Ph+ ALL. The 5 pivotal phase II studies collected data from 481 treated subjects with leukaemia. The company behind Sprycel is carrying out trials in children with newly diagnosed Ph+ ALL and in relapsed and/or refractory Ph+ ALL according to the agreed PIP. A total of 5 trials were agreed to in PIP, EMEA-000567-PIP01-09-M04 (Table 3-21).

Table 3-23: Comparison of authorised and prospective tyrosine kinase inhibitors for children with Ph+ALL

	Glivec (Novartis Europharm Ltd) Imatinib Initial MA granted in Nov 2001 for Adults with r/r CML, indication for ALL in adults granted in Sep 2006, indication for paediatric ALL granted on June 2013		**Sprycel (Bristol-Myers Squibb Pharma EEIG)** Dasatinib Initial centralised MA granted in Nov 2006 for Adult with newly diagnosed or imatinib resistant CML or Ph+ALL resistant to prior therapy, paediatric development Phase III		**Iclusig (Incyte Biosciences UK Ltd)** Ponatinib Initial MA granted in July 2013 for Adult with CML or Ph+ ALL who are resistant or intolerant to other TKIs or who have the T315I mutation.,	
	Healthy Volunteers	**Affected patients**	**Healthy Volunteers**	**Affected patients**	**Healthy Volunteers**	**Affected patients**
Studies not initiated but agreed to in PIPs	**N/A**	**N/A**	**N/A**	**N/A**	**N/A**	**Studies for EMEA- 001186-PIP01-11-M01** • OL, single- agent, dose- escalation, MC trial to investigate tolerability, S and A of ponatinib in the paediatric population from 1 year to <18 years of age with malignant disease for which no effective treatment is known and with an expansion cohort of the paediatric population with BCR-ABL translocation- positive ALL. • R, MC, dose- comparative, double- blind trial to investigate the S, A and E of ponatinib as add- on to standard therapy in the paediatric population from 1 year to <18 years of age with relapsed or refractory BCR-ABL translocation- positive ALL
Phase II **(Phase III if specified)**	**N/A**	**Studies: ADE10, AFR09, AIT04, AAU2, ADE04, AJP01, AUS01, 0109 & 0114** • 9 studies in adults • N = 738 adults with newly diagnosed and r/r Ph+ ALL • Haematological response, OS, EFS and TTP **STI571AIT07** • OL, R, S & E trial • 128 children with Ph+ ALL • DFS **STI571I2301** • OL, non-randomised feasibility and toxicity pilot study • 92 children and adolescents < 22 years with Ph+ ALL received imatinib • EFS	**N/A**	**Study CA180015** • OL, SA, MC, S & E and PK study • Adults with Ph+ blast phase CML (n=42) or Ph+ ALL (N=36) who were intolerant, resistant or who had progression to imatinib • Haematological and cytogenetic response rates **Study CA180-372 (Ongoing)** • MC, historically controlled, S & E study • 75 newly diagnosed children with Ph+ ALL • EFS at 3 years **Study CA180-226** • OL, non-randomised, parallel assignment (3 cohorts) study • 145 children with newly diagnosed CML but relapsed Ph+ALL • Complete Hematologic Response (CHR) rate **Study AALL0622** • OL, SA, F, S & E phase II/III study • 195 newly diagnosed patients aged 2 to 30 years with Ph+ ALL, (children n = 58) • AEs and toxicity, EFS at 3 years	**N/A**	**Study AP24534-10-201** • Pivotal, OL, single arm non-comparative 6 cohort study • 444 adults with CML in CP, AP, or BP; or Ph+ ALL. Patients either: 1) had disease that was resistant to, or were intolerant to, therapy with either dasatinib or nilotinib; or 2) had the BCR-ABL T315I mutation. • Endpoints for Ph+ ALL; Major hematologic response (consisting of CHR & No Evidence of Leukaemia (NEL)
Supportive Studies	**N/A**	**Physiologically based PK (PBPK) model based on 4 PK studies.** N = 67 patient; CML (n =46), Ph+ ALL (12), Other haematological malignancies (n=9)	**N/A**	**N/A**	**N/A**	**N/A**
		Total Exposed = 1025 of which; Adults 738 and Children 287		**Total Exposed = 493 of which; Adults 215 and Children 278**		**Total Exposed (Until Nov 2017) = 444 Adults**

Abbreviations: A, activity; AEs, Adverse Events; ALL, acute lymphoblastic leukaemia; AP, accelerated phase; BP, blast phase,; CHR, complete haematological response rate; CML, chronic myeloid leukaemia; CP, chronic phase; CT, chemotherapy; DFS, disease free survival; E, efficacy; EFS, event free survival; F, feasibility; MA, Marketing Authorisation; MC, multicentre; NEL, no evidence of Leukaemia; OL, open-label; OS, overall survival ; PD, pharmacodynamics; Ph+, Philadelphia chromosome-positive; PIP, paediatric investigation plan; PK, pharmacokinetics; R, randomized; S, safety; SA, single-arm; TKI, tyrosine Kinase inhibitor; TTP, time to progression ;

Blincyto and Kymriah are compared in Table 3-24. Blincyto and Kymriah represent efforts by the industry to develop new drugs in novel drug categories for relapsed or refractory B-ALL. Blincyto was authorised under, conditional approval, in November 2015 for adults with relapsed and/or refractory B-ALL and is currently carrying out trials in children. Kymriah is not yet authorised in the EU although a marketing authorisation application has been submitted. The Blincyto indication in adults was based on 3 phase II trials and a historical comparator study. The primary endpoint used in phase II trials was complete remission (CR) and complete remission with partial haematological recovery (CRh*). Survival based endpoints, namely relapse free survival (RFS) and OS were included as secondary endpoints. The paediatric indication will be based on 3 phase II trials and 1 phase III randomised controlled trial. Phase II trials including an expanded access protocol trial (Study 20130320) that will assess long term safety and efficacy and a trial in infants with MLL rearranged ALL.

Three phase II and 2 phase III studies are ongoing for Kymriah, of which 4 are safety and efficacy trials and 1 (study CCTL019A2205B) is a long term follow up study. The CDP reflects the targeted indication age group (r/r B-ALL from 3 to 25 years) since all trials recruited children and young adults up 25 years old. Study CCTL019A2205B may accept adults older than 25 and elderly patient, that will be recruited from Kymriah studies in relapsed or refractory DLBCL (another prospective indication for Kymriah). Study endpoint for Kymriah included are complete remission (CR) and complete remission with Incomplete Blood Count Recovery, as well as RFS.

Table 3-24: Comparison of two novel compounds in different categories for paediatric patients with relapsed and/ or refractory acute lymphoblastic leukaemia

	Blincyto (Amgen Europe B.V) Blinatumomab Initial MA granted in Nov 2015 for adults with r/r B-ALL. Paediatric development Phase III		**Kymriah (Novartis Europharm Limited)** Tisagenlecleucel Ongoing MA application for B-ALL	
	Healthy Volunteers	**Affected patients**	**Healthy Volunteers**	**Affected patients**
Phase II	**N/A**	**Study MT103-202** • OL, MC, SA, S, E & tolerability study • Adults with B - ALL with positive MRD after standard chemotherapy. N = 21 • CR/CRh* **Study MT103-206** • OL, MC, S, E & tolerability exploratory study • Adults with r/r B - ALL. N=36 • CR/CRh* **Study MT103-211** • OL, MC, S & E main study • Adults with r/r B-ALL. N = 184 • CR/CRh* **Study MT103-205** (EudraCT Number: 2010-024264-18) • SA, MC, E, S & tolerability study • Paediatric and Adolescent Patients with r/r B-ALL. N=70 • DLT, CR, OS **Study 20130320 (ongoing** - EudraCT Number: 2014-001700-21) • MC, OL, Expanded Access Protocol • Paediatric and Adolescent Subjects with r/r B-ALL. N=40 • ADRs, CR, MRD, RFS, OS **Study NL59901.078.17 (ongoing -** EudraCT Number: 2016-004674-17) • F, S, E pilot study • Infants with newly diagnosed MLL-rearranged acute lymphoblastic leukemia. N=30 • Incidence of AEs	**N/A**	**Study CCTL019B2202 (Ongoing)** EudraCT Number: 2013-003205-25 • SA, MC, S & E study • Paediatric patients with relapsed and refractory B- ALL. N=65 • ORR, CR. Cri **Study CCTL019B2205J (Ongoing)** EudraCT Number: 2015-003736-13 • SA, MC, S & E study • Paediatric patients with relapsed and refractory B- ALL. N=50 • ORR, CR. Cri **Study CCTL019B2101J/CHP-959 (Ongoing)** EudraCT Number: 2017-002849-30 • S & E study • Children and young adult patients with a recurrent form of B-cell leukaemia and lymphoma. N=86. • Number of patients with severe AEs at 24 weeks
Phase III	**N/A**	**Study 20120215 (ongoing)** EudraCT Number: 2014-002476-92 • OL, E, S & tolerability RCT comparing blinatumomab to standard of care chemotherapy • Paediatric Subjects with High-risk First Relapse ALL. N =320 • EFS, OS, MRD & Cumulative incidence of relapse	**N/A**	**Study CCTL019A2205B (Ongoing)** EudraCT Number: 2014-001673-14 • Long Term Follow up study (15 years) • Children, adults and elderly who have been treated Novartis CTL019. N=550 • Proportion of patients with new malignancies & hematologic disorder, incidence/exacerbation of pre-existing neurologic disorder or prior rheumatologic or other autoimmune disorder, **Study CCTL019B2001X (Ongoing)** EudraCT Number: 2016-001991-31 • Expanded treatment protocol to collection additional S &E data • Children and adolescent patients with a recurrent form of B-cell acute lymphoblastic leukaemia. N=55 • Safety, CR, Cri, relapse free survival
Supportive / Other Studies	**N/A**	**Study 20120310** - Historical comparator study to provide haematological remission rates and survival among adult patients with Ph- r/r B-ALL with standard of care chemotherapy **Total Exposed = 701, of which; Adults 241 and Children 460**	**N/A**	**N/A** **Total Exposed = 806 (Children, adults and elderly)**

Abbreviations: ALL, acute lymphoblastic leukaemia; OL, open-label; SA, single-arm; S, safety; SR, standard risk; MC, multicentre; PK, pharmacokinetics; Ph-, Philadelphia chromosome-negative; E, efficacy; R, randomized; Pop, population; PD, pharmacodynamics; CAR, chimeric antigen receptor; LL, lymphoblastic lymphoma; MA, Marketing Authorisation Cri, Complete Remission with Incomplete Blood Count Recovery; CRh*, complete remission with partial haematological recovery

Chapter 4
Discussion

4.1 Emerging patterns in the development of medicines in paediatric ALL

The optimal treatment for acute lymphoblastic leukaemia (ALL) in children has been in development for over 50 years, yet unmet medical needs remain. The emerging patterns in the development of medicines to treat paediatric ALL identified in the research may be listed as follows:

A. General observations from the clinical development programs of authorised and prospective products

1. *The development of new dosage forms for children is a trend used by industry to bring to market products that improve practicality of administration, patient acceptability and treatment compliance.*

Example (i) The development of an intravenous busulfan formulation represented a significant logistical improvement over the 2mg busulfan tablet formulation that was authorised prior to 2003. Both adults and children undergoing busulfan based conditioning prior to hematopoietic stem cell transplantation (HSCT) had to swallow a large number of tablets, up 30 tablets per day, to reach the high therapeutic doses required.

Example (ii) The development of off-the-shelf oral liquids of methotrexate and mercaptopurine potentially facilitates the maintenance treatment phase in ALL protocols that is administered an outpatient basis. Such paediatric formulations are advantageous over splitting tablets and unlicensed extemporaneously prepared liquid formulations due to more accurate dosing, better product stability and avoiding potential exposure to cytotoxics during the compounding process.

2. *The development of new formulations of the old armamentarium is a strategy used by industry to overcome acute toxicities and improve patient safety.* New formulations were observed in authorised and prospective products. Example (i) The Asparaginase enzyme has been a component of multidrug chemotherapy in therapeutic use since 1966 with two preparations derived from *E. coli* or *E. chrysanthemi* approved for human use (Batool et al, 2016). The development of PEGylated *E. coli* derived asparaginase (Oncaspar) was advantageous due to a longer circulation time that allowed for a once daily administration and reduced immunogenicity when compared to native *E. coli* asparaginase preparations. Two other prospective asparaginase products are in development, asparaginase enclosed in red blood cells (Graspa) and calaspargase pegol, and aim to continue to improve on the reduced immunogenicity and better pharmacokinetics established by Oncaspar over previous formulation of asparaginase depleting agents. Example (ii) New formulations of established products were observed in development, such as liposomal vincristine, liposomal cytarabine and daunorubicin as a combination product and liposome–encapsulated doxorubicin–citrate complex that are currently in phase II and phase III development. A combination product consisting of liposomal formulations of cytarabine and daunorubicin was observed in phase I development.

3. *New active substances tended to be directed at specific population subgroups with poor outcome. Post authorisation procedures may be used to extend indications if clinical trials in appropriately selected patient cohorts have been carried out.* Example (i) Imatinib was authorised for elapsed and/or refractory chronic myeloid leukaemia (CML) in adults in 2001, the through post authorisation variation application the company sought indications in *de novo* CML in adults, Philadelphia chromosome

positive (Ph+) ALL in adults then children and also in other cancer areas. Example (ii) Clofarabine and nelarabine were authorised in 2006 and 2007 respectively as monotherapy for B-ALL and T-ALL in second or greater relapse. Both clofarabine and nelarabine are being studied as part of combination chemotherapy and the companies may pursue first and second line indications. Example (iii) The specificity of new active substances is mirrored in the development phase where new active substance under investigation target specific ALL mutations or certain cell surface markers, for example lestaurtinib for infants with Mixed-lineage leukaemia (MLL)-rearranged MLL rearranged ALL, ruxolitinib for Janus kinase (JAK) signalling mutations in B-ALL and blinatumomab for CD20 positive relapsed and/or refractory B-ALL. The indications of future products are likely to more specific than current products. The development of increasingly specific therapy may be a consequence of advancements in the biological understanding of ALL where several district subtypes based on specific genomic mutation are now known (Dizon et al, 2016).

4. *The CDP used to support the positive opinions of authorised products were diverse. The diversity of CDPs and strategies used by companies to gain market access highlights the flexibility of the EU regulatory framework.*
Example (i) The CDP required for authorisation varied from extensive (10 adult trials, 2 paediatric studies and 1 pharmacokinetic modelling study) in Glivec, a product seeking both a first and a second line indication to minimal (1 adult and 1 paediatric trial) in Atriance, a product seeking third line indication in a small patient population under exceptional circumstance.
Example (ii) Well-established use applications with bibliographic dossiers (n=2) and

hybrid applications (n=2) were observed in 4 products. Products like Jylamvo (methotrexate liquid) and Xaluprine (mercaptopurine liquid) were based on bioequivalence (BE) studies rather than full clinical development programs (CDPs), indicating that the development of new formulation of established agents by the pharmaceutical industry is less resource intensive than investing in new products.

5. *Companies that are developing new active substances and that intend to target similar indications based on the same pathology, may benefit from applying for groups of indications through single applications rather than extending indications through successive variation applications.*

Example (i) Tyrosine kinase inhibitors (TKIs) for Ph+ ALL were developed in a drug generations framework. Glivec was the first in class TKI that was first developed for CML and later for Ph+ ALL in adults and then in children. The total number of safety and efficacy trials to support Glivec's initial authorisation and ALL indications was 15 trials (3 for adult CML, 9 for adult ALL and 3 for paediatric ALL) which is more than Sprycel at 11 trials (5 for adult CML, 1 for adult ALL and 5 for paediatric ALL) and Iclusig at 3 trials (1 trials for adult CML and ALL, 2 trials for paediatric ALL)

6. *Companies who opt to use single applications for multiple indications rather than extending indications in a stepwise manner could larger clinical trials with parallel arms to reflect their different target cohorts rather than carrying out multiple smaller single arm trials to further optimised their CDPs and registration strategy.*

Example (i) Iclusig was authorised in 2013 for adults with CML or Ph+ ALL who are resistant or intolerant to other TKIs or who have the T315I mutation. To support the Iclusig indication the company presented a single pivotal study with 6 cohorts that recruited 444 patients with CML and Ph+ ALL. This approach differed to the first TKI

for Ph+ ALL, Glivec, where the CDP for each successive indication consisted of several smaller single arm trials,

B. How drugs in the development phase will affect treatment protocols

Drugs in the development phases will not significantly alter first line ALL treatment protocols in children. Prospective products for *de novo* Philadelphia chromosome negative (Ph-) ALL will likely be used as add-on therapies to the chemotherapeutic backbone established in past large-scale trials carried out by prominent cancer study groups. In the future clinicians will use targeted molecules in addition to established chemotherapy induce the best possible outcomes in their patients. This calls for more precise diagnosis of ALL at the molecular level so that the best treatment possible is chosen for each patient based on the genetic mutation expressed.

For Ph+ ALL, second generation TKIs are being explored as alternative to imatinib for children who are intolerant or who relapse despite optimum use of first generation TKIs and for children with specific mutations associated with the Philadelphia chromosome. Dasatinib is being investigated as an alternative to imatinib in first line and second line treatment protocols for children with Ph+ ALL. Ponatinib is being investigated as a second line treatment alternative to other TKIs. Nilotinib is being investigated in phase I trials for r/r Ph+ ALL. Bosutinib (Bosulif) is another TKI authorised in the EU although no plans for use in children with Ph+ ALL were found. The development of successive generations of TKIs for use in children is justified since emergent TKI resistance and development of the T315I mutation with imatinib is a major reason for treatment failure in patients with Philadelphia positive leukemic disease (Cortes et al, 2012; Bernt & Hunger, 2014).

Second line treatment protocols for Ph- ALL are less rigid and more open to change. Apart for traditional combination chemotherapy based on small molecules, new drug categories and strategies are being explored. The new drug categories are monotherapy biologicals, monotherapy antibody-drug conjugates and immunotherapy based on CAR-T cells and represent a paradigm shift away from the traditional multidrug chemotherapy. The same strategies are being studied in Ph+ ALL as third line treatment or greater in cases of multiple TKI failures.

Small molecules will likely remain the most prominent overall drug category in use for paediatric ALL. Small molecules authorised in the last 15 years and in development are diverse and include broad cytotoxics such as clofarabine or nelarabine, as well as reformulations of established agents and several targeted protein kinase inhibitors. Clofarabine and nelarabine were initially authorised as third line monotherapy and are being studied as combination chemotherapy for first and second line use. Other long-established compounds are being made safer through reformulations to serve as additions to established first line regimens. Target small molecules are being developed for first line and second line ALL, including TKIs but also JAK inhibitors, proteasome inhibitors and BCL inhibitors among others. Three small molecules were investigated as adjuvants rather than active treatment. Pentoxifylline was investigated as a potentiator of anticancer medicines in the induction phase while allopurinol and 6TG were investigated as pharmacokinetic interactor to raise blood levels of the cytotoxic compounds used in the maintenance phase. Even if these trials prove to be successful, these were small and isolated trials that would unlikely lead labelling change.

New biologicals were observed to a lesser degree than small molecules, although will still have a role in prospective treatment protocols. Blinatumomab was a promising

biological medicine observed that showed positive efficacy and a favourable safety profile in paediatric trials in r/r ALL (Ribera, 2017). Other biological medicines investigated for children with ALL are monoclonal antibodies, epratuzumab and rituximab and new formulations of asparaginase depleting agents. Biological based products were also observed in the form of antibody conjugates, a new category of drugs that includes antibody drug conjugates (ADCs) and immunotoxins. The hypothesis behind ADCs is that such products combine the ability of monoclonal antibodies (mAbs) to target specific cellular receptors with the cytotoxic potency of small molecules (Weiner, 2015). Inotuzumab ozogamicin is a promising ADC being studied children after exceptional activity was demonstrated in adults with r/r ALL (Bhojwani et al, 2017). ADCs are emerging other cancer treatment areas apart from ALL (Diamantis & Banerji, 2016).

A sharp rise of ATMP based trials was observed in the last five years. Gene therapy-based chimeric antigen receptor (CAR) T cells and innovative cellular based therapies were the main contributors to the volume of trails investigating ATMPs. Tisagenlecleucel is a first-in-class CAR-T therapy to treat relapsed C19 positive B-ALL that has been approved by the FDA. An EU marketing authorisation application has been lodged for tisagenlecleucel and will likely be the first of many CAR-T cell-based therapies to be introduced to clinical practice in Europe. CAR-T cell therapies are of significance since they are the first commercialised products that offers a potentially curative option to patients with ALL and a corresponding explosion of interest in CAR-T cell-based therapies has been reported in literature (Ma et al, 2016; Lim & June, 2017). CAR-T cell products are being developed for other cancers apart from ALL (Pettitt et al, 2018).

In HSCT, trials investigating ATMP as off-the-shelf donor replacements or as HSCT adjuvants were observed. ATMP based adjuvants aim to improve patient outcome through enhanced engraftment and suppression or treatment of graft versus host disease (GvHD). Some of the major challenges, namely engraftment failure and the occurrence of GVHD, associated with HSCT at present times are being addressed by adjunctive treatment with ATMPs. Academia related entities sponsored 4 out of the 7 ATMP based studies in HSCT furthering the notion that academia and esteemed university hospitals remain important stakeholders in the development of innovative medicines for cancer especially in the novel and complex area of ATMP development. Literature suggests that lack of regulatory expertise and commercialisation foresight may possibly hinder the entry of gene and cell-based therapies to market (de Wilde et al, 2016; Elsanhoury et al, 2017)

C. Observations from clinical trials

The majority of drugs under investigation are following the traditional drug development framework where phase I trials are followed by phase II trials and in some cases phase III trials. Phase I trials aimed to establish the safety and toxicity profile as well as the treatment dose. The endpoints used to meet these aims where the maximum tolerated dose, dose limiting toxicities and recommended phase 2 dose. Pharmacokinetic (PK) and pharmacodynamic (PD) endpoints were also observed, and efficacy related endpoints were observed in 49 out of 78 phase I trials. The design of choice was the single arm, open label non-randomised trials. Randomisation and parallel assignment were only observed in BE studies. Phase 1 trials tend have a mixed population afflicted by different diseases. The studied population tended to be narrower in late clinical development. A number of products that were studied in different blood

malignancies in the early development phase were later authorised only in a single condition.

Phase II and phase III trials had similar objectives and endpoints focussing on efficacy and safety. The most common endpoints were safety related endpoints such as adverse event characterisation and frequencies and efficacy related endpoint such minimal residual disease (MRD), event free survival (EFS) and overall survival (OS). Phase II and phase III trials differed on the basis of patient recruited where phase III trials recruited more patients than phase II trials and study design where phase III were more likely to be randomised, controlled and have parallel assignment. Measures of GVHD, engraftment, OS and mortality related endpoints such as treatment related mortality (TRM) and non-relapsed mortality (NRM), were most prevalent endpoints observed in trails investigating products for HSCT through all phases.

Few sponsors did not follow the traditional drug development framework and combined clinical trial phases. Phase I/II were observed more frequently than phase II/III clinical trials. Combining phases I and II may allow typical research questions associated with early drug development to be answered faster or with less patients. In the phase I part of the clinical trial the toxicity profile and optimum dose is determined, then in the phase II part, patients would usually receive the MTD determined in phase I and investigators collect exploratory efficacy data from the same patient cohort.

Affected patients were recruited for all oncologic clinical trials. The testing of cytotoxic drugs in healthy volunteers is considered to be unethical. The only exception was 2 sets bioequivalence (BE) studies to development new formulations. The CDP of Jylamvo and Xaluprine involved BE studies that recruited healthy adult patients rather than

affected paediatric patients even though the proposed indication involved children. This decision was considered to be acceptable by the CHMP since the applicants could justify that study results from studies in adults could be extrapolated to children. To minimise harm to healthy volunteers few doses were administered days apart.

Patient survival-based endpoints were observed more frequently tumour-based endpoints. This in line with Committee for Human Medicinal Products (CHMP) and Food and Drug Administration (FDA) guidance on clinical endpoints to support the approval of anticancer medicines. Survival related endpoints (overall survival, event free survival and disease-free survival) were the most common endpoint in phase II and phase III trials for ALL. Measurement of MRD was observed as an indicator of morphological response together with endpoint such as complete remission (CR). The choice of endpoint should reflect the objective of the trial which is often correlated to the trial phase[63]. For example, overall survival is an excellent indicator of overall benefit in large trials however is not used in phase I studies.

4.2 Future work and Limitation of this study

This study focused on the development of medicines for childhood ALL, the patterns observed may not necessarily apply to development trends in other therapeutic areas. Future work could focus on other leukemic diseases such as acute or chronic myeloid leukaemia or other prevalent paediatric cancers such as brain and spinal cord tumours, neuroblastoma, Wilms tumour and lymphoma. The method could be applied to cancer in adults or non-malignant diseases. The development of a multivariate regression

[63] European Medicines Agency and CPMP. Note for Guidance on Good Clinical Practice (CPMP/ICH/291/95) - ICH Topic E 6, Step 5, Consolidated Guideline [Online]. London(UK): European Medicines Agency; c2006 [Updated 1998 Mar 01: cited 2018 May 25]. Avialable from URL: http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002877.pdf

model could be of potential interest to investigate the relationship between observed trends. Statistical testing could be applied to numbers of recruited patients across drug categories or trial phases or to other factors to establish if differences observed were significant or random chance.

This study is limited to the quality of the data sources used. All data sources were publicly available documents and databases. Missing information in study records was noted, this included absent endpoints and clinical trials without a designated phase. Missing information was most prevalent in old study records and records of trials carried out exclusively in countries outside the EU and USA. One study record with conflicting information was noted. A degree of uncertainty in the result is possible since trials with missing or conflicting information were not included in the analysis. Two clinical trial databases were used to provide a comprehensive picture of drugs in the development phase. EudraCT and clinicaltrials.gov are administered by two different regulatory regions and do not have the same framework for data elements. Two examples of different data classification included the drug category and the trial status. Clinical trials.gov classifies investigation medicinal products (IMPs) as either a drug or a biological while the EU clinical trial register classifies IMPs as actives substances of chemical origins, of biological/ biotechnological origin or as ATMPs with further subcategories for ATMPs. The same applies for trials status where Clinical trials.gov uses 9 different descriptors for trial status when compared to the EU clinical trial which uses 4. Lack of standardisation was mitigated, where possible by adopting common framework to harmonised data capture for both data sources.

Data quality was also a concern when retrieving study information from early European public assessment reports (EPARs) since a lack of consistency among study details

reported was observed. The same sentiment was expressed by Barbui et al in 2011 (Barbui et al, 2011) on EPARs for psychiatric medicines approved by the EMA. EPARs were first published in 1995 (Papathanasiou et al, 2016) and have developed over time to be more usable, transparent and appropriately detailed.

Trials selection was carried out by a single person rather than a panel and while the utmost care was taken to appropriately include and excluded trials according to the criteria established the possibility of errors cannot be excluded. A list of all excluded trials has been provided to allow post study review.

4.3 Conclusion

This study aimed to identify emerging patterns in the development of paediatric oncology medicinal products for acute lymphoblastic leukaemia through a review of clinical development programs. Nine new centrally authorised products for paediatric ALL, authorised between October 2005 and November 2017, were considered for this project. Three products were new active substances and 6 products were new formulations or paediatric friendly dosage forms of known active substances that still contributed to the advancement of ALL treatment. Drugs in the development phase were identified for 13 PIPs and 227 trials registered in the EU clinical trial register and the United States national library of medicine database of clinical trials. Prospective treatment protocols were proposed based 35 different products in the phase II and phase III development.

It is perhaps the first study to focus specifically on emerging patterns in the clinical development for medicinal products used in paediatric ALL and contributes to the understanding of how different pharmaceutical companies have approached paediatric

drug development in ALL. Insight and understanding of drug development and regulatory science is useful to pharmaceutical industries who must prove safety and efficacy through a well devised program of clinical trials prior to marketing their products. Trends in the number of trials, number of patients recruited, and endpoints used successfully in previous marketing authorisation applications as discussed, could complement the scientific guidance available for prospective applicants of anti-cancer medicines for children in the EU.

The study is also of interest to regulators of medicines whose members are tasked with risk-benefit based evaluation of data provided by companies during marketing authorisation applications. Through examining emerging patterns and trend in drug development, regulators can continue to update and devise new technical guidelines for industry and provide better scientific advice, which is free for questions relating to paediatric development.

Academia and cancer research groups have an active role in clinical trials investigating treatment for paediatric ALL. This study may help non-industrial stakeholders interpret and apply regulatory requirements needed to adequately demonstrate safety and efficacy to university hospitals or cancer research groups sponsored trials so that useful data derived from such studies could be used to support the new labelling claims of medicinal products. This is beneficial to avoid wasting stakeholder resources on similar trials running in parallel and to avoid unethically subjecting children to repeated trials investigating the same thing. This study is useful to clinicians since it provides foresight of drugs in the development phase through the prospective treatment protocols proposed.

In conclusion better and more effective programs of clinical studies could reduce unnecessary and avoidable delays in the authorisation of medicines for children with ALL to the benefit of patients.

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Appendices

Appendix 1

Centrally authorised products indicated for the treatment of paediatric acute lymphoblastic leukaemia and products indicated as conditioning treatment prior haematopoietic stem cell transplantation

Medicine Name	Active Substance	ATC code	Marketing Authorisation Holder	Authorisation date	Full Indication	Condition Approval	Exceptional Circumstance	Orphan
Atriance	nelarabine	L01BB07	Novartis Europharm Limited	22/08/2007	Nelarabine is indicated for the treatment of patients with T-cell acute lymphoblastic leukaemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) whose disease has not responded to or has relapsed following treatment with at least two chemotherapy regimens. Due to the small patient populations in these disease settings, the information to support these indications is based on limited data.	no	yes	yes
Busilvex	busulfan	L01AB01	Pierre Fabre Médicament	09/07/2003	Busilvex followed by cyclophosphamide (BuCy2) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation (HPCT) in adult patients when the combination is considered the best available option. Busilvex following fludarabine (FB) is indicated as conditioning treatment prior to haematopoietic progenitor cell transplantation (HPCT) in adult patients who are candidates for a reduced-intensity conditioning (RIC) regimen. Busilvex followed by cyclophosphamide (BuCy4) or melphalan (BuMel) is indicated as conditioning treatment prior to conventional haematopoietic progenitor cell transplantation in paediatric patients.	no	no	no
Evoltra	clofarabine	L01BB06	Genzyme Europe B.V.	29/05/2006	Treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients 21 years old at initial diagnosis.	no	yes	no
Glivec	imatinib	L01XE01	Novartis Europharm Ltd	07/11/2001	Glivec is indicated for the treatment of adult and paediatric patients with newly diagnosed Philadelphia-chromosome (bcr-abl)-positive (Ph+) chronic myeloid leukaemia (CML) for whom bone-marrow transplantation is not considered as the first line of treatment; adult and paediatric patients with Ph+ CML in chronic phase after failure of interferon-alpha therapy, or in accelerated phase or blast crisis; adult and paediatric patients with newly diagnosed Philadelphia-chromosome-positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy; adult patients with relapsed or refractory Ph+ ALL as monotherapy; adult patients with myelodysplastic / myeloproliferative diseases (MDS / MPD) associated with platelet-derived growth factor receptor (PDGFR) gene re-arrangements; adult patients with advanced hypereosinophilic syndrome (HES) and / or chronic eosinophilic leukaemia (CEL) with FIP1L1-PDGFRa rearrangement. The effect of Glivec on the outcome of bone-marrow transplantation has not been determined. Glivec is indicated for:	no	no	no

Appendix 1

Centrally authorised products indicated for the treatment of paediatric acute lymphoblastic leukaemia and products indicated as conditioning treatment prior haematopoietic stem cell transplantation

Medicine Name	Active Substance	ATC code	Marketing Authorisation Holder	Authorisation date	Full Indication	Condition Approval	Exceptional Circumstance	Orphan
					the treatment of adult patients with Kit (CD 117)-positive unresectable and / or metastatic malignant gastrointestinal stromal tumours (GIST); the adjuvant treatment of adult patients who are at significant risk of relapse following resection of Kit (CD117)-positive GIST. Patients who have a low or very low risk of recurrence should not receive adjuvant treatment; the treatment of adult patients with unresectable dermatofibrosarcoma protuberans (DFSP) and adult patients with recurrent and / or metastatic DFSP who are not eligible for surgery. In adult and paediatric patients, the effectiveness of Glivec is based on overall haematological and cytogenetic response rates and progression-free survival in CML, on haematological and cytogenetic response rates in Ph+ ALL, MDS / MPD, on haematological response rates in HES / CEL and on objective response rates in adult patients with unresectable and / or metastatic GIST and DFSP and on recurrence-free survival in adjuvant GIST. The experience with Glivec in patients with MDS / MPD associated with PDGFR gene re-arrangements is very limited (see section 5.1). Except in newly diagnosed chronic phase CML, there are no controlled trials demonstrating a clinical benefit or increased survival for these diseases.			
Jylamvo	methotrexate	L01BA01	Therakind Limited	29/03/2017	Oncology: Jylamvo is indicated Maintenance treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children aged 3 years and over.	no	no	no
Oncaspar	pegaspargase	L01XX24	Baxalta Innovations GmbH	14/01/2016	Oncaspar is indicated as a component of antineoplastic combination therapy in acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years, and adult patients.	no	no	no
Spectrila	asparaginase	L01XX02	Medac Gesellschaft fuer klinische Spezialpraeparate mbH	14/01/2016	Spectrila is indicated as a component of antineoplastic combination therapy for the treatment of acute lymphoblastic leukaemia (ALL) in paediatric patients from birth to 18 years and adults.	no	no	no
Tepadina	thiotepa	L01AC01	Adienne S.r.l.	15/03/2010	In combination with other chemotherapy medicinal products: with or without total body irradiation (TBI), as conditioning treatment prior to allogeneic or autologous haematopoietic progenitor cell transplantation (HPCT) in haematological diseases in adult and paediatric patients; when high dose chemotherapy with HPCT support is appropriate for the treatment of solid tumours in adult and paediatric patients.". It is proposed that Tepadina must be prescribed by physicians experienced in conditioning treatment prior to haematopoietic progenitor cell transplantation.	no	no	yes
Xaluprine	6-mercaptopurine monohydrate	L01BB02	Nova Laboratories Ltd	15/03/2010	Xaluprine is indicated for the treatment of acute lymphoblastic leukaemia (ALL) in adults, adolescents and children.	no	no	yes

Appendix 2

Prospective products for the treatment of paediatric acute lymphoblastic leukaemia and prospective products for conditioning/adjunctive treatment prior to haematopoietic stem cell transplantation from paediatric investigation plans

Active Substance	ALL Indication(s) targeted by the PIP	PIP applicant	Decision number	PIP number	Pharmaceutical form(s)	Condition(s)/indication(s)	Route(s) of administration	Decision date
Autologous T cells transduced with lentiviral vector containing a chimeric antigen receptor directed against CD19 (CTL019)	Treatment of CD19+ B cell acute lymphoblastic leukaemia (ALL) in paediatric patients whose disease is refractory to a standard chemotherapy regimen, relapsed after stem cell transplantation (SCT) or are ineligible for allogenic SCT	Novartis Europharm Limited	P/0270/2017	EMEA-001654-PIP01-14-M02	Cell suspension for infusion	Treatment of B cell acute lymphoblastic leukaemia/lymphoblastic lymphoma	Intravenous use	22/09/2017
Autologous T cells transduced with retroviral vector encoding an anti-CD19 CD28/CD3-zeta chimeric antigen receptor	Treatment of relapsed or refractory B-precursor acute lymphoblastic leukaemia (r/r ALL)	Kite Pharma EU B.V	P/0238/2017	EMEA-001862-PIP01-15	Dispersion for infusion	Treatment of acute lymphoblastic leukaemia	Intravenous use	09/08/2017
Blinatumomab	Treatment of children with previously untreated high-risk first relapse of B precursor acute lymphoblastic leukaemia	Amgen Europe B.V.	P/0014/2016	EMEA-000574-PIP02-12-M01	Powder for solution for infusion	Treatment of acute lymphoblastic leukaemia	Intravenous use	29/01/2016
Cyclophosphamide	Treatment of paediatric malignant diseases including haematological malignancies (including acute leukaemia, malignant non-Hodgkin lymphoma, Hodgkin disease) as well as soft tissue sarcoma (including rhabdomyosarcoma, osteosarcoma and Ewing sarcoma), neuroblastoma and retinoblastoma	Keocyt SAS	P/0021/2012	EMEA-000530-PIP02-11	Soluble tablets	Treatment of malignant diseases	Oral use	27/01/2012
Expanded donor-derived allogenic T cells transduced with the retroviral vector expressing the transgenes for inducible caspase9 and the truncated CD19 selectable marker (BPX-501) -	Treatment of immunodeficiency after mismatched, related, allogeneic transplantation in paediatric patients with malignant and non-malignant disorders amenable to haematopoietic stem cell transplantation	Bellicum Pharma Ltd.	P/0138/2017	EMEA-001869-PIP01-15	Dispersion for infusion	Adjunctive treatment in haematopoietic stem cell transplantation	Intravenous use	07/06/2017
Herpes simplex 1 virus thymidine kinase and truncated low affinity nerve growth factor receptor transfected donor lymphocytes	Adjunctive treatment in haematopoietic cell transplantation	MolMed S.p.A.	P/0057/2014	EMEA-001370-PIP02-13	Cell suspension for infusion	Adjunctive treatment in haematopoietic cell transplantation	Intravenous use	06/03/2014

Appendix 2

Prospective products for the treatment of paediatric acute lymphoblastic leukaemia and prospective products for conditioning/adjunctive treatment prior to haematopoietic stem cell transplantation from paediatric investigation plans

Active Substance	ALL Indication(s) targeted by the PIP	PIP applicant	Decision number	PIP number	Pharmaceutical form(s)	Condition(s)/indication(s)	Route(s) of administration	Decision date
Navitoclax (ABT-263)	Treatment of acute lymphoblastic leukaemia	Abbott Laboratories	P/135/2011	EMEA-000478-PIP01-08-M01	Powder for solution, age appropriate liquid formulation; Capsule; Soft tablet	Treatment of acute lymphoblastic leukaemia, Treatment of non-Hodgkin lymphoma	Oral use	10/06/2011
T-lymphocytes enriched leukocyte preparation depleted ex vivo of host host-alloreactive T cells using photodynamic treatment (ATIR101)	Adjunctive treatment to a haploidentical haematopoietic stem cell transplantation with CD34+ selected cells, in patients with a haematological malignancy, for the reduction of incidence and severity of graft versus host disease and for the reduction of mortality due to infection and relapse	Kiadis Pharma Netherlands B.V.	P/0078/2017	EMEA-001980-PIP01-16	Cell suspension for infusion	Adjunctive treatment in haematopoietic stem cell transplantation for a malignant disease	Intravenous use	16/03/2017
Treosulfan	Treosulfan in combination with a fludarabine-containing myeloablative conditioning regimen to treat a paediatric patient with a malignant disease, which requires an allogeneic haematopoietic stem cell transplant	Medac Gesellschaft fuer klinische Spezialpraeparate mbH	P/0197/2017	EMEA-000883-PIP01-10-M04	Powder for solution for injection / infusion	Conditioning treatment prior to haematopoietic-progenitor-cell transplantation	Intravenous use	14/07/2017
Dasatinib	Treatment of Philadelphia chromosome (BCR-ABL translocation)-positive (Ph+) acute lymphoblastic leukaemia.	Bristol-Myers Squibb Pharma EEIG	P/0118/2013	EMEA-000567-PIP01-09-M04	Film-coated tablet, age-appropriate oral formulation	Treatment of Philadelphia-chromosome (BCR-ABL translocation)-positive acute lymphoblastic leukaemia, Treatment of Philadelphia-chromosome (BCR-ABL translocation)-positive chronic myeloid leukaemia	Oral use	02/05/2013
L-asparaginase encapsulated in erythrocytes	Treatment of patients with acute lymphoblastic leukaemia	Erytech pharma S.A.	P/0267/2017	EMEA-000341-PIP02-09-M04	Suspension for injection, suspension for infusion	Treatment of acute lymphoblastic leukaemia	Intravenous use	04/09/2017
Momelotinib	Treatment of paediatric patients with newly diagnosed acute lymphoblastic leukaemia with a Janus kinase (JAK)-activating mutation in combination with chemotherapy	Gilead Sciences International Ltd	P/0157/2015	EMEA-001656-PIP01-14	Film-coated tablet; Age-appropriate oral dosage form	Treatment of acute lymphoblastic leukaemia, Treatment of essential thrombocythaemia, Treatment of polycythaemia vera, Treatment of post-essential thrombocythaemia myelofibrosis, Treatment of post-polycythaemia vera myelofibrosis	Oral use	10/07/2015
Ponatinib	For the treatment of the paediatric population with Ph+ ALL who are resistant or intolerant to prior TKI therapy	Incyte Biosciences UK Ltd	P/0127/2017	EMEA-001186-PIP01-11-M01	Coated tablet; Capsule, hard; Age-appropriate formulation	Treatment of acute lymphoblastic leukaemia, Treatment of chronic myeloid leukaemia	Oral use	05/05/2017

Appendix 3

List of clinical trials excluded categorised by exclusion criteria and year

Trials excluded prior to review			
Exclusion criteria	**Years**	**Number of trials**	**NCT Number / EudraCT Number**
Observational studies	Pre – 2000	6	NCT00996047, NCT00002485, NCT00899652, NCT00003291, NCT00899899, NCT00919425
	2000 to 2006	23	NCT00005881, NCT00026780, NCT01678508, NCT01005277, NCT00898079, NCT00898404, NCT00482352, NCT00402935, NCT00330538, NCT00900120, NCT00085176, NCT00897767, NCT00505141, NCT01663129, NCT03356262, NCT00898469, NCT00897507, NCT00920738, NCT00920842, NCT00896766, NCT01556386, NCT00897325, NCT00899366
	2007 to 2017	46	NCT00437060, NCT00526084, NCT00898755, NCT00566566, NCT00674193, NCT00898612, NCT00918658, NCT00900445, NCT00801346, NCT00957736, NCT00993135, NCT01476462, NCT00897078, NCT00993694, NCT00949052, NCT01104324, NCT01016379, NCT01089907, NCT01150669, NCT01142427, NCT01653613, NCT01896752, NCT01295476, NCT01185886, NCT01886651, NCT01298388, NCT01324336, NCT01393249, NCT01520246, NCT01540578, NCT01533168, NCT01619124, NCT01553162, NCT01581528, NCT01626183, NCT01625143, NCT01629745, NCT02993978, NCT01119586, NCT01793233, NCT02303522, NCT03035344, NCT03372642, NCT02847130, NCT02995525, NCT03359421
		Total N = 75	
Intervention was a device, a dietary supplement, or an educational program	Pre – 2000	0	N/A
	2000 to 2006	1	NCT00055718
	2007 to 2017	10	NCT00713505, NCT00782145, NCT00949117, NCT01766804, NCT01901367, NCT02410252, NCT02559557, NCT03192683, NCT03176849, NCT03223753
		Total N = 11	
Behavioural therapy	Pre – 2000	0	N/A
	2000 to 2006	1	NCT00268528
	2007 to 2017	9	NCT01253720, NCT00902213, NCT03132948, NCT01503632, NCT02300961, NCT02361047, NCT03187977, NCT03157323, NCT03234777
		Total N = 10	
Trials excluded after to review			
Exclusion criteria	**Years**	**Number of trials**	**NCT Number / EudraCT Number**
Studies listed in the EU clinical trial Database	Pre – 2000	0	N/A
	2000 to 2006	3	NCT00930098, NCT00287105, NCT00315705
	2007 to 2017	20	NCT01423500, NCT00991744, NCT00866281, NCT00991133, NCT01279096, NCT01228331, NCT01431664, NCT01471782, NCT01460160, NCT01195480, NCT01906671, NCT02065869, NCT02227108, NCT02228096, NCT02435849, NCT02393859, NCT02625480, NCT02808442, NCT03289455, NCT03236857
		Total N = 23	
Studies used to support the applications of current CAP	Pre – 2000	3	NCT01177371, NCT00002970, NCT00003545
	2000 to 2006	9	*EudraCT Number:* 2004-001647-30, 2004-001853-27 NCT00004932, NCT00042341, NCT00022737, NCT00049569, NCT00244829, NCT00192673, NCT00693602
	2007 to 2017	7	*EudraCT Number:* 2006-003180-31, 2008-006300-27, 2010-018418-53, 2012-001477-82 2015-001172-21, 2015-004902-41 NCT01066468
		Total N = 19 (CT.gov n = 11; EU-CTR n = 8)	

Appendix 3

List of Clinical Trials excluded categorised by exclusion criteria and year

Trials excluded after to review			
Exclusion criteria	**Years**	**Number of trials**	**NCT Number / EudraCT Number**
Studies to optimise the safety and efficacy of chemotherapy regimens based on authorised products	Pre – 2000	21	NCT00002499, NCT00002471, NCT00002553, NCT00002502, NCT00018954, NCT00411541, NCT00002673, NCT00165087, NCT00002744, NCT00002756, NCT01230983, NCT00002785, NCT00002812, NCT00002816, NCT00003437, NCT00003217, NCT00003671, NCT00003728, NCT00015873, NCT00019409, NCT01225874
	2000 to 2006	24	*EudraCT Number:* 2004-001738-17, 2004-001861-17, 2005-004599-19, 2005-000658-56 NCT00005603, NCT00005585, NCT00005596, NCT00005945, NCT00430118, NCT00005977, NCT00613457, NCT00054327, NCT00014469, NCT00131053, NCT00967057, NCT00764907, NCT00022126, NCT00343369, NCT00112567, NCT00186875, NCT00075725, NCT00096135, NCT00103285, NCT00400946
	2007 to 2017	23	*EudraCT Number:* 2007-004021-19, 2007-004090-26, 2009-011454-17, 2010-020924-22, 2011-003815-46, 2012-000067-25, 2011-005023-40, 2011-003430-13, 2014-001561-27, 2007-004270-43, 2015-002734-41 NCT00381680, NCT00550992, NCT01953770, NCT00537030, NCT00707083, NCT00846703, NCT00816049, NCT00819351, NCT00866307, NCT02011022, NCT01190930, NCT03007147
		Total N = 68 (CT.gov n =53; EU-CTR n =15)	
Studies to optimise the selection of bone marrow donors and bone marrow transplantation procedures	Pre – 2000	14	NCT00060255, NCT00002534, NCT00003187, NCT00002718, NCT00025545, NCT00005622, NCT00008164, NCT00003116, NCT00005641, NCT00003270, NCT00003335, NCT00003398, NCT00005804, NCT00005854
	2000 to 2006	11	NCT00004255, NCT00290641, NCT00265837, NCT01423747, NCT00118326, NCT00084695, NCT00534118, NCT00079404, NCT00608517, NCT00309907, NCT00412360
	2007 to 2017	9	EudraCT Number: 2005-005106-23, 2007-004517-34 NCT00004255, NCT00290641, NCT00265837, NCT01423747, NCT00118326, NCT00084695, NCT00534118, NCT00079404, NCT00608517, NCT00309907, NCT00412360
		Total N = 34(CT.gov n = 32; EU-CTR n = 2)	
Studies investigating products associated with HSCT but not part conditioning treatment prior to haematopoietic-progenitor-cell transplantation or as adjunctive treatment in haematopoietic stem cell transplantation	Pre – 2000	7	NCT00002456, NCT00002790, NCT00003538, NCT00003883, NCT00014391, NCT00005802, NCT00004230
	2000 to 2006	14	NCT00010283, NCT00045292, NCT00053157, NCT00089037, NCT00078858, NCT00079222, NCT00253552, NCT00134017, NCT00089141, NCT00096096, NCT00105001, NCT00245115, NCT00357084, NCT00410657
	2007 to 2017	7	*EudraCT Number:* 2006-006577-25 NCT00382109, NCT00489203, NCT00769613, NCT01427881, NCT01655875, NCT02728700
		Total N = 28 (CT.gov n = 27; EU-CTR n= 1)	

Appendix 3

List of Clinical Trials excluded categorised by exclusion criteria and year

Trials excluded after to review			
Exclusion criteria	**Years**	**Number of trials**	**NCT Number / EudraCT Number**
Studies investigating conditions falling outside the WHO 2016 definition of ALL	Pre – 2000	4	NCT00002750, NCT00002621, NCT00003073, NCT00112593
	2000 to 2006	11	*EudraCT Number:* 2005-001067-64, 2006-004710-41 NCT00020111, NCT00006246, NCT00002757, NCT00058461, NCT00324779, NCT00087009, NCT00101205, NCT00112619, NCT00057811
	2007 to 2017	21	*EudraCT Number:* 2008-002288-14, 2009-014462-26, 2010-019224-31, 2012-002934-35, 2013-000341-39, 2013-000390-70, 2012-005538-12, 2010-018980-41, 2013-000018-39, 2014-000652-28, 2014-002172-92, 2015-001901-15, 2015-004625-14, 2015-000827-94, 2017-002146-72, 2014-005066-30 NCT00526292, NCT01817075, NCT02989675, NCT03369847, NCT03318393
		Total N = 36 (CT.gov n = 18; EU-CTR n = 18)	
Studies investigating products to mitigate or manage side effect of antitumor treatment	Pre – 2000	2	NCT00003805, NCT00003938
	2000 to 2006	12	NCT00004132. NCT00186901, NCT00022035, NCT00006348, NCT00020527, NCT00036712, NCT00066599, NCT00066248, NCT00080873. NCT00365768, NCT00349024, NCT00886496
	2007 to 2017	14	*EudraCT Number:* 2007-001430-14, 2007-000230-39, 2009-010700-28, 2014-003303-30, 2014-000328-47 NCT00369564, NCT00509691, NCT00728585, NCT01100658, NCT01305200, NCT01371656, NCT02314273, NCT01656512, NCT01506453
		Total N = 28 (CT.gov n = 23; EU-CTR n = 5)	
Information on study endpoints was missing	Pre – 2000	17	NCT00002638, NCT00002961, NCT00002738, NCT00006451, NCT00005852, NCT00003243, NCT00003962, NCT00003408, NCT00003661, NCT00003887, NCT00003396, NCT00003913, NCT00053131, NCT00003874, NCT00008190, NCT00004232, NCT00290628
	2000 to 2006	4	NCT00005606, NCT00005892, NCT00005946, NCT00055653
	2007 to 2017	0	N/A
		Total N = 21(CT.gov n = 21; EU-CTR n = 0)	
Other studies not relevant to the study	Pre – 2000	2	NCT00003933, NCT00006042
	2000 to 2006	3	NCT00056069, NCT00070421, NCT00305851
	2007 to 2017	14	EudraCT Number: 2008-008278-29, 2011-005790-23, 2013-001236-21, 2013-004773-27, 2016-002372-27 NCT00726934.NCT02544789, NCT01053494, NCT01216332, NCT01492569, NCT02551718, NCT02618109, NCT03043430, NCT03040570
		Total N = 19 (CT.gov n = 14; EU-CTR n = 5)	

Appendix 4

Clinical Development Programs for Centrally Authorised Products indicated for the treatment of paediatric ALL and products indicated as conditioning treatment prior to HSCT

Glivec® (Imatinib)

Novartis Europharm Ltd

This is a summary of the CDP in support of the ALL indication in adults and children.

Glivec was first authorised in November 2001 as second line treatment for chronic myeloid leukaemia in adult.

The extension of induction for Glivec for "Treatment of adult patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy and of adult patients with relapsed or refractory Ph+ ALL as monotherapy" was granted in September 2006 through a type II variation Glivec-H-C-406-II-0031.

The extension of the indication for the treatment of paediatric patients with newly diagnosed Philadelphia chromosome positive acute lymphoblastic leukaemia (Ph+ ALL) integrated with chemotherapy was granted in June 2013 through Glivec-H-406-II-80.

The legal basis used was Article 16 of Commission Regulation (EC) No 1234/2008 ('Prior Approval' procedure for major variations of type II).

CDP for Adult ALL Indication - Glivec-H-C-406-II-0031

Healthy Volunteers	Affected patients
N/A	**Study 03001 - Phase I** • *Objective/Design:* Dose escalating pilot study • *Administration:* Imatinib mono-therapy induction at 300 mg to 1000 mg • *Population:* 20 relapsed/refractory patients with Ph+ALL (n=10) and CML-LBC (n=10) • *Endpoints:* o Efficacy Endpoint: Anti-leukaemic activity by decrease in peripheral WBC counts and percent Ph+ cells in bone marrow
N/A	**Study ADE10 - Phase II** • *Objective:* To investigate efficacy/safety of imatinib mono-therapy induction compared to standard induction chemotherapy followed by combination of imatinib with chemotherapy as consolidation • *Design:* Open label, randomized, multicentre, two arm, controlled study • *Population:* 55 newly diagnosed PH+ ALL patients over 55 years old (28 patients in imatinib arm & 27 patients in controlled arm) • *Administration/ Duration:* 600mg mg daily for 28 days • Endpoints: o Efficacy Endpoint: Haematological remission rate, remission duration, minimal residual disease, relapse rate, DFS, OS

Healthy Volunteers	Affected patients
N/A	**Study AFR09 - Phase II** • *Objective:* To investigate imatinib post induction therapy combined with steroids • *Design:* Open-label, non-randomized, multi-centre study • Population: 30 newly diagnosed Ph+ ALL patient over 55 • *Administration/Duration:* 600 mg daily combined with intermittent steroids for 2 months • Endpoints: o Efficacy Endpoint: Complete haematological response, Complete Molecular response, DFS, OS
N/A	**Study AIT04 - Phase II** • Objective: To verify the activity and safety of imatinib induction in combination with steroids (prednisone) • Design: Open-label, non-randomized, multi-centre study • Administration: 800 mg daily • Population: 19 newly diagnosed Ph+ ALL patient over 55 • Endpoints: o Efficacy Endpoint: Complete haematological response, Complete Molecular response, DFS, OS

N/A	**Study AAU02 - Phase II**
	
	• *Objective:* Pilot study of imatinib in combination with induction chemotherapy
	• *Design:* open label, non-randomized
	• *Administration/Duration:* Imatinib 600mg daily for 7 days with chemotherapy
	• *Population:*
	  o 12 newly diagnosed patient with Ph+ ALL
	  o 9 relapsed/refractory patients with Ph+ ALL (n=7) and CML-LBC (n=2)
	• *Endpoints:*
	  o Efficacy Endpoint : haematological response, cytogenetic response

N/A	**Study ADE04 - Phase II** • *Objective:* To determine the safety and efficacy of imatinib and minimal residual disease after induction therapy • Design: Open label, multi-centre, non-randomized study • *Administration/Duration:* 400-600mg imatinib 18 days post induction for 28 days • *Population:* 92 newly diagnosed Ph+ ALL (n=88) or CML-LBC (n=4) • *Endpoints:* o Efficacy Endpoint: Conversion rate to MRD negativity, time to MRD negativity, remission induction rate, DFS, OS,

Healthy Volunteers	Affected patients

N/A	**Study AJP01 - Phase II**
	
	• *Objective:* to evaluate imatinib combined with dose-intensive chemotherapy
	• *Design:* Open-label, non-randomized, multi-centre
	• *Administration:* 600mg imatinib combined with induction and consolidation chemotherapy
	• *Population:* 80 newly diagnosed Ph+ ALL
	• *Endpoints:*
	  o Primary: complete remission rate.
	  o Secondary: Remission duration, DFS, OS, the conversion rate and time to minimal residual disease negativity

N/A	**Study AUS01 - Phase II**
	
	• *Objective:* To determine the clinical efficacy and safety of the intensive hyper- CVAD regimen with imatinib
	• *Design:* Uncontrolled study
	• *Administration:* Imatinib 400 mg daily for 14 days per hyper-CVAD regimen cycle
	• *Population:*
	  o 32 newly diagnosed patients with Ph+ ALL
	  o 5 refractory patients with Ph+ ALL
	• *Endpoints:*
	  o Efficacy Endpoint: Overall response rate, event-free survival, and survival

N/A	**Study 0109 - Phase II** • *Objective:* To evaluate the clinical efficacy and safety of imatinib in CML in accelerated phase and relapse/refractory Ph+ ALL patients • *Design:* Open label, non-randomized, multi-centre study • *Administration:* Imatinib 400-600 mg daily • Population: 56 relapse/refractory with Ph+ALL (n=48) and CML-LBC (n=8), 18/56 over 55 years old • *Endpoints:* o Efficacy Endpoint: Confirmed hematological response, duration of hematological response, cytogenetic response
N/A	**Study 0114 – Phase II** • *Objective:* To provide patients with Ph+ CML in accelerated phase (AP) or relapsed/refractory Ph+ ALL with expanded access to imatinib until the product was commercially available • *Design:* Open-label, non-randomized, multi-centre, expanded access study • Administration: Imatinib 600 mg daily • *Population:* 353 relapsed/refractory Ph+ ALL or CML-LBC patients, 128/353 Over 55 years old • *Endpoints:* o Efficacy Endpoint: Time to progression

Haematological response (to be confirmed after >4 weeks)	Complete haematological remission (CHR)	Bone marrow cellularity and blast count < 5%, no circulating peripheral blood blasts, ANC ≥ 1.5 x 109 /L, Platelet count ≥ 100 x 109 /L, and no evidence of extra-medullary involvement
	No evidence of leukaemia	Blast count < 5%, no circulating peripheral blood blasts, ANC ≥ 1.0 x 109 /L, platelet count > 20 x 109 /L (platelet transfusion independent and no evidence of bleeding), and no evidence of extramedullary involvement
	Return of chronic phase haematopoiesis/partial response (PR)	For a PR, only the first criterion below were to be fulfilled. For a return to chronic phase haematopoiesis, all of the following criteria were to be fulfilled: percentage of peripheral blasts in blood or bone marrow < 15%, percentage of blasts plus promyelocytes in the peripheral blood or bone marrow < 30%, and peripheral basophils < 20%.
	Marrow response (marrow-CR)	Decrease in marrow blasts to either no more than 5% or between 5 to 15%, regardless of the peripheral-blood cell counts
	Morphologic response	(1) M1, 0% to 5% bone marrow blast cells; (2) M2, more than 5% to 25% bone marrow blast cells; or (3) M3, more than 25% bone marrow blast cells
Cytogenetic response		Percentage of Ph chromosome positive metaphases in bone marrow and was defined as follows: complete (0% Ph-positive cells); major (1-35%); minor (36-65%); minimal (66-95%); none (96-100%).
Complete molecular remission		Reverse transcriptase polymerase chain reaction (RT-PCR) negativity in addition to haematological criteria for complete haematological remission

CDP for Paediatric ALL Indication - Glivec-H-406-II-80	
Healthy Volunteers	**Affected patients**
N/A	**Physiologically based PK (PBPK) model** • *Objective:* o To predict paediatric AUC at steady-state using PBPK approach based on imatinib clearance in adult population, then compare the results with the experimentally observed AUC values, with specific focus on children age 1 year and older. o To predict imatinib plasma concentration-time profiles in plasma and tissue in paediatric subjects, and to assess the effect of paediatric growth processes using a PBPK model o To evaluate factors influencing imatinib exposure in paediatric patients **Pooled popPK** • **STI571A0103 -** Phase I dose-finding study to determine the safety, tolerability, PK/PD and efficacy of imatinib in paediatric patients with Ph+ leukaemia • **STI57103001 -** Phase I dose-finding study to determine the safety, tolerability, PK and PD profiles of imatinib in patients with CML resistant to interferon-alpha (IFN) • **STI571A2108 -** Phase II non-randomised single arm study to determine the response rate of imatinib in paediatric CML and delineate its toxicity and PK in paediatric patients. • **STI571A2110 -** Non-randomised, open-label PK study in which patients diagnosed with CML, Ph+ ALL or other imatinib indicated haematological disorders between the ages of 1 to 4 years • *Population:* Total 67 patient; CML (n =46), Ph+ ALL (12) , Other haematological malignancies (n=9
N/A	**STI571AIT07 - Phase II (Supportive)** • *Objective:* To determine whether the addition of imatinib to standard chemotherapy extended DFS in paediatric patients with Ph+ ALL. • *Design:* Randomized, open label study • *Administration:* Imatinib 300mg/m^2/day, median exposure duration 121 days • *Population*: Newly diagnosed Ph+ patients (n = 160); stratified by risk; good risk (n = 90), poor risk (n=70). Total patient exposed to imatinib n = 128 • *Endpoints* o Primary endpoint: Disease free survival (DFS) o Secondary endpoints: Event free survival (EFS), Overall Survival (OS), Comparison of safety (Imatinib + chemo vs chemo alone), Molecular response as a surrogate for DFS, Minimal Residual Disease (MRD)

N/A	**STI571I2301 Phase II (Pivotal)** • *Objective:* To determine the feasibility of patient accrual and toxicity of an intensified chemotherapeutic regimen (including imatinib for Ph+ ALL patients) for treatment of children and adolescents with VHR ALL • *Design:* Non-randomised, open label study • *Administration***:** 340 mg/m2/d or 230 mg/m2/d where doses were calculated according to body surface area. Patients who could not tolerate the higher dose were given the lower dose • *Population:* 160 paediatric VHR ALL patient of which 92 were Ph+ patients and received imatinib • *Endpoints:* o Primary Endpoint: Event-free survival (EFS) o Secondary Endpoints: OS, exposure-response of imatinib, safety and tolerability of imatinib + chemo

Endpoint Definitions for Glivec-H-406-II-80

Primary efficacy endpoint	EFS	Defined as the time between study entry and the earliest of the following events: leukemic relapse (BM, CNS, testicular, or other) at any site, secondary malignancy, or death.
Secondary endpoint	OS	Defined as the time between study entry and death due to any cause

Atriance® (Nelarabine)

Novartis Europharm Limited

This is the CDP in support of the initial Marketing Authorisations for Atriance (nelarabine solution for infusion) granted on 22/08/2007 under 'Exceptional Circumstances'.

The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

Healthy Volunteers	Affected Patients
n/a	**Phase I Dose response studies** All were open-label, dose escalating safety and PK study to determine the MTD of nelarabine Patient were adults and children with different haematological malignancies Study PGAA1001 (n = 93 patients: 65 adult; 28 paediatric patients) Study PGAA1002 (n = 27 patients: 17 adult; 10 paediatric patients) Study PGAA1003 (n = 48 patients: 46 adults; 2 paediatric patients)
n/a	**Study PGAA2001 - Phase II Main study** • *Design:* two-stage, open label, multicentre paediatric clinical trail • *Aims:* To evaluate nelarabine in paediatric patients (≤21 years of age at diagnosis) with refractory or relapsed T-lineage acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LBL) • *Objectives:* To evaluate the efficacy (response rate: CR and PR, complete and partial response) of nelarabine administered as a one-hour infusion daily for 5 days in pediatric patients with relapsed or refractory T-ALL or T-NHL. Secondary objectives were to evaluate the safety, duration of response and time to response in paediatric patients and to correlate the pharmacology of nelarabine, and ara-G nucleotides with clinical response • *Administration:* 1-hour infusion of nelarbine at 4 different dose levels for 5 consecutive day • *Duration:* Cycles were to be repeated every 21 days or until the occurrence of one or more of the following: disease progression, unmanageable toxicity, continued treatment with nelarabine was no longer deemed beneficial, or treatment had continued for two years. • Population: N = 70 patients with T-ALL or T-NHL • Endpoints: o Primary: Response rate i.e Complete Response (CR), CR*, CRh* and partial response (PR) o Secondary: Duration of response, Time to Response, Overall survival (OS)

Healthy Volunteers	Affected Patients
N/A	**Study PGAA2002 – Phase II Main study** • *Design:* open label, multicentre clinical trial in adults • *Aims:* To evaluate nelarabine in adult patients (≥16 years of age at diagnosis) with refractory or relapsed T-lineage acute lymphoblastic leukaemia (ALL) or lymphoblastic lymphoma (LBL) • *Objectives:* To determine the efficacy (response rate) of nelarabine given at a dose of 1500 mg/m2/day on an alternate day schedule (days 1, 3, 5) in adult patients with refractory or relapsed T-ALL or LBL. Secondary objectives were to evaluate the safety of nelarabine administered on this schedule, the impact of nelarabine therapy on survival. Time to response was also evaluated. • *Administration:* IV infusion over 2 hours at a dosage of 1500 mg/m2 on days 1, 3 and 5 of a 21-day cycle • *Population:* N= 39 adult patients with T-ALL or LBL • *Endpoints* o Primary: (CR, CR* and PR). o Secondary: Duration of response, time to response and overall survival

Additional Non-Pivotal small safety studies

Seven additional studies submitted in support of nelarabine:

- CALGB69803 - Phase I
- MDACC 86 - Phase II
- CALGB59901 - Phase II
- SWOG S0010 - Phase II
- COG AALL00P2 - Phase II
- MDACC 430 - Phase II
- TRC9701 - Phase II

Endpoints and definitions for CDP of nelarabine

Primary endpoint	Complete Response (CR)	Defined as bone marrow blast counts ≤5%, no evidence of disease, and full recovery of peripheral blood counts (i.e., ANC >1500/µl, platelets >100 000/µl, Hgb ≥10 g/dl for patients less than 2 years of age, Hgb ≥11 for patients ≥2 years of age).
	CR*	Defined as bone marrow blast counts ≤5% and no other evidence of disease but incomplete haematologic recovery.
	Partial response (PR)	A partial bone marrow response was defined as bone marrow blast percents less than or equal to 25% occurring at any time on the study.
	CRh*	Defined as bone marrow blast counts ≤5%, no other evidence of disease, and partial recovery of peripheral blood counts (i.e., ANC >500/µl, platelets >50 000/µl, Hgb ≥ 7 g/dl).
Secondary outcome measure	Duration of response	Measured from the date of response assessment to relapse, death, or last date of contact. Treatment with additional anti-cancer therapy was not a criterium for termination of response. Relapse was determined by occurrence or reoccurrence of disease in bone marrow, peripheral blood blasts, CSF or extramedullary disease
	Time to Response	Defined as the elapsed time from treatment start to response date.
	Overall survival (OS)	Defined as the elapsed time from treatment start date to death. Patients who were alive at the end of the study reporting period were censored at date of last contact.

Busilvex® (Busulfan concentrate for solution for infusion)

Pierre Fabre Medicament

This is the CDP in support in support of initial Marketing Authorisations for Busilvex (busulfan solution for infusion) granted 11/07/2003 and Type II Variation application for Busilvex for an extension of indication to the paediatric population granted 27/10/2005.

The Legal Basis used was so-called "bibliographical application", in accordance with directive 65/65/EEC, article 4.8 (a) ii. The initial MA application was for new intravenous formulation based on oral busulfan.

Healthy Volunteers	Affected patients
N/A	**OMC BUS 2 – Phase I** • *Objective:* Intra-patient comparison of the pharmacokinetics of Busilvex with oral busulfan • *Design:* Prospective, single arm, Open Label, Multicentre Safety, PK Study • *Administration & Sampling:* Bu Dose 1 IV, Doses 2 – 16 Oral. Sampling: Dose 1, 5 (rich data) • *Population:* N=15 patients with HSCT • *Endpoints:* Dose-normalised ratio of i.v. AUC at first dose, v. oral AUC at steady-state

N/A	**Amendment 4 of studies OMC-BUS 3 and OMC-BUS 4 – Phase II**
	• *Objective:* Intra-patient comparison of the pharmacokinetics of Busilvex with oral busulfan.
	• *Design* Pharmacokinetic substudy (after conduct of OMC BUS 3 and 4)
	• *Administration & Sampling*: Bu Dose 1 Oral, Doses 2 - 16 I.V. Sampling: Dose 1, 9 (rich data) dose 13 (LS)
	• *Population:* N= 12
	  o 3 patients of OMC-BUS 3 [Autologous HSCT]
	  o 9 patients of OMC-BUS 4 [Allogeneic HSCT]
	• *Endpoints:* Dose-normalised ratio of i.v. AUC at first dose, v. oral AUC at steady-state

N/A	**OMC-BUS 3 – Phase II (Main Study)**
	• *Objective:* Assess the efficacy and safety of Busilvex as conditioning treatment
	• *Design:* Prospective, single arm, open-label, multicentre trial, uncontrolled phase II
	• *Administration & Sampling* Bu Doses 1 through 16: I.V. Sampling: Dose 1, 9 (rich data) dose 13 (LS)
	• *Population:* N = 42 patients candidates for Autologous HSCT
	• *Endpoints:*
	  o Short-term
	  ▪ Myeloablation
	  ▪ Time to Engraftment
	  o Long Term
	  ▪ Disease-free survival (DFS)
	  ▪ Relapse
	  ▪ Survival and transplant-related mortality

Healthy Volunteers	Affected patients

N/A	**OMC-BUS 4 – Phase II (Main Study)**
	
	• *Objective:* Assess the efficacy and safety of Busilvex as conditioning treatment
	• *Design:* Prospective, single arm, open-label, multicentre trials, uncontrolled phase II
	• *Administration & Sampling:* Bu Doses 1 through 16: I.V. Sampling: Dose 1, 9 (rich data) dose 13 (LS)
	• *Population:* N=62 patients candidates Allogeneic HSCT
	• *Endpoints*
	  ○ Short-term
	  ▪ Myeloablation
	  ▪ Time to Engraftment
	  ○ Long Term
	  ▪ Disease-free survival (DFS)
	  ▪ Relapse
	  ▪ Survival and transplant-related mortality

N/A	**OMC-BUS-6 and OMC-BUS-7 - Phase II (Supportive studies)** • Design: Prospective, single-centre open-label uncontrolled safety and efficacy studies • *Administration:* Bu 16-dose regimen, IV • Population: N 23 autologous (OMC-BUS 6) or allogeneic (OMC-BUS 7) • Endpoints: Same as Main studies

N/A	**OMC BUS 5 – Phase II**
	
	• *Main Objective:* Define an appropriate dosing schedule for Busilvex in children (as well as supporting efficacy and safety)
	• Design: Prospective, open label, preliminary(dose-finding) study
	• *Administration:* Dose 1 through 16: I.V
	• Population: N=24 paediatric patients candidates for Allogeneic HSCT
	• Endpoints
	  ○ Target AUC range
	  ○ Myeloablation
	  ○ Engraftment
	  ○ Estimated probability of survival

N/A	**Study F60002 IN 1 01 G0-Phase II**
	
	• Objective: Pivotal study for efficacy and safety (as well as confirming the kinetics i.e attainment of the therapeutic window through a weight-based dosing regimen, without dosage adjustment)
	• Design: Prospective, open label study
	• *Administration:* IV Bu (standard 16-dose regimen)
	• *Population:* N= 55 paediatric patients mixed autologous or allogeneic transplants
	• *Endpoints:*
	  ○ Target AUC range
	  ○ Myeloablation
	  ○ Engraftment
	  ○ Event free survival and overall survival

Evoltra ® (clofarabine)

Genzyme Europe B.V.

The is the CDP for support of the initial Marketing Authorisations for Evoltra (clofarabine solution for infusion) granted on 29/05/2006 under 'Exceptional Circumstances'

The legal basis for this application refers to Article 8.3(i) of Directive 2001/83/EC, as amended - complete and independent application.

Healthy Volunteers	Affected Patients
N/A	**Study DM93-036 – Phase I** • *Aims:/Objectives:* To determine the MTD and toxicity profile of clofarabine • *Design:* Open-label, dose escalating, adult study • *Administration:* 1.5 to 55 mg/m2 clofarabine IV for 1 hour every day for 5 consecutive days every 3 to 4 weeks • *Population:* N = 51 patients with solid tumours or hematologic malignancies who failed standard therapy • *Endpoints:* MTD
N/A	**Study ID99-383 - Phase I** • *Aims/ Objectives:* To Determine the MTD; safety and pharmacokinetics of clofarabine in children • *Design:* open-label, non-comparative, dose-escalation, paediatric study • *Administration:* 11 to 70 mg/m2 clofarabine IV for 1 to 3 hours every day for 5 days every 2 to 6 weeks • *Population:* N = 25 paediatric patients (17 with ALL and 8 with AML) with relapsed or refractory leukaemia • *Endpoints:* MTD & DLT

N/A	**Study CLO-212 - phase II**
	
	• *Objectives:* To determine overall remission (OR) rate. Secondary objectives included documentation of CR, CRp, and of partial response (PR) rates, as well as duration of remission and overall survival (OS), and the safety profile and tolerability of clofarabine for this dosing regimen in paediatric population
	• *Design:* non-randomized, open-label, single-arm study in paediatric study
	• *Administration:* IV 52 mg/m2 day for 5 consecutive days repeated every 2 to 6 weeks
	• *Duration:* Treatment was continued until disease relapse for a potential maximum of 12 cycles
	• Population N= 61 patients ≤ 21 years of age
	• Endpoints:
	  ○ Primary: (CR, CRp and PR).
	  ○ Secondary: Duration of response, time to response and overall survival

Endpoint definitions

Complete remission (CR)	Patients who met each of the following criteria: • No evidence of circulating blasts or extramedullary disease • An M1 bone marrow (≤ 5% blasts) • Recovery of peripheral counts (platelets ≥ 100 x 109 /L and ANC ≥ 1.0 x 109 /L)
Complete remission in the absence of total platelet recovery (CRp)	Patients who have met all of the criteria for a CR except for recovery of platelet counts to > 100 x 109 /L
Partial remission (PR)	Patients who met each of the following criteria: • Complete disappearance of circulating blasts • An M2 bone marrow (≥ 5% and ≤ 25% blasts) and appearance of normal progenitor cells • An M1 marrow that does not qualify for CR or CR

ONCASPAR® (Pegaspargase)

Baxalta Innovations GmbH

This is a summary of the CDP in support of Initial MA (14/01/2016). The legal basis for this application refers to Article 8.3 of Directive 2001/83/EC - complete and independent application

Only studies in support of *de novo* ALL are presented. An additional 8 trials that recruited 293 adults and children with relapsed or refractory haematological malignancies were present. Study CCG-1991 study the safety of pegaspargase in 2957 patients

Healthy Volunteers	Affected patients
N/A	**Study CCG-1962 # – Phase II** • Multicenter, randomized safety, efficacy, and pharmacokinetics study • *Design:* Randomised comparison of PEG-L-Asparaginase and Native E. coli Asparaginase, o Two treatment groups (PEG-ASNase or native ASNase) • *Administration:* Oncaspar (2,500 IU/m2 i.m.) on Day 3 of Induction and Day 3 of each Delayed Intensification. vs Native E coli asparaginase (6,000 IU/m2 i.m.) 3 times weekly for 9 doses during induction and for 6 doses during each delayed intensification phase. • Duration of main phase: 18 months • Population: N=118 Total patients (randomized to Oncaspar: 59/118), Population = children with newly diagnosed, previously untreated SR-ALL • *Endpoints:* o EFS (Primary Endpoint) o Antiasparaginase antibody ratio (Co-Primary endpoint)
N/A	**Study CCG-1961@ - Phase III** • Interventional, open label, multicentric, partially randomized efficacy study • *Hypothesis:* Superiority of Increased (containing Oncaspar) and/or Prolonged Duration Intensification Chemotherapy over Standard Intensification Chemotherapy in Rapid Early Responder (RER) high risk ALL patients • 2 × 2 factorial design to the 4 regimens (study arms) • *Administration:* Single injection of Oncaspar (2.500 IU/m2) during induction and Delayed Intensifications vs. 9 injections of native E-coli L-asparaginase (6.000 IU/m2) during induction and 6 during each Delayed Intensification • Duration of main phase: 2 years for girls, 3 years for boys • N= 2077 (total enrolled with N=163 evaluable pts), Population = Children with newly diagnosed ALL with high risk features • *Endpoints:* o EFS (Primary Endpoint) o OS (Co-Primary endpoint)

N/A	**Study DFCI-87-001 ** - Phase III** • A multicentre, open label, In vitro and in vivo sub-studies • *Design:* randomized comparison of E. coli ASNase, Erwinia ASNase or PEG-ASNase - efficacy equivalence trail between the 3 asparaginases in 3 treatment groups • Administration: Single injection during a 5-day investigational window before treatment start. 4.6 yrs follow up • Duration of main phase: 5-day investigational window • N = 344 (enrolled) with N=251 evaluable of which randomized to Oncaspar: 84/251 • Population =Children with newly diagnosed ALL • Endpoints: o EFS (*Primary endpoint)* o In vitro mean total cell kill rate (*Primary endpoint)* o Co-Primary endpoints: ▪ In vivo reduction(%) in PB absolute blast count ▪ In vivo reduction(%) in BM leukemic infiltrate ▪ Leukemic cell kill rate ▪ Patients with leukemic events/Patients in continuous CR
N/A	**Study DFCI-91- 01 - - Phase III** • A Multicentre open-label, randomized, controlled efficacy and safety study • *Hypothesis:* (1) To determine whether Oncaspar was associated with decrease toxicity compared to native *E.coli* Lasparaginase. (2) Impact of asparaginase tolerance on long-term outcome • Parallel Assignment to 4 treatment groups • *Administration:* Pts in Oncaspar treatment group received 2.500 IU/m2 Oncaspar (15 doses) throughout treatment phases. • Duration of main phase: 2 years from achievement of CR • N=377 (enrolled) with N=325 evaluable of which randomized to Oncaspar: 106/325 • Population =newly diagnosed children with ALL • *Endpoints:* o 5-y EFS (Primary Endpoint)
N/A	**Study DFCI-05-001[$]** Population: N = 551 newly diagnosed ALL patients from 1 to 18 years of age with 232 were randomized to PEG-ASP (Oncaspar) **Study AALL07P4[$]** Population: N =135 newly diagnosed patients from 1 to 30 years of age with NCI HR B-precursor ALL (HRALL) with 43 receiving Oncaspar

@ CCG-1961 was submitted in the format of bibliographical references.

CCG-1962 is a sub study of sub-study of CCG-1952

** The data from this sub-study are recorded as Study ASP-301

$ Two additional studies were presented in support of the first line indication

Spectrila® (Recombinant L-asparaginase produced in E. coli)

Medac

Spectrila is a recombinant L-asparaginase produced in E. coli and was licensed on 14/01/2016 on the legal basis of Article 8.3 of Directive 2001/83/EC - complete and independent application.

Healthy Volunteers	Affected patients
N/A	**STUDY MC-ASP.4/ALL – Phase II** • *Objectives:* To compare the PK/PD, efficacy and safety of recombinant ASNase versus Asparaginase medac during induction treatment in children with *de novo* ALL • *Design:* Single centre, double-blind, controlled, parallel group phase II trial • *Administration:* 5.000U /m (I.V infusion) once every 3 days for 8 doses over 22 days • *Population: De novo* ALL patients (1 to 18 years), N= 32 (total) of which 16 allocated to r-ASNase Medac • *Endpoint:* o Primary Endpoints: AUC 0-72h o Secondary endpoints: (1) PK endpoints; Cmax, Tmax, λz (terminal elimination rate constant), t1/2λz (terminal elimination half-life), (2) trough levels of asparaginase activity in serum (3) serum and cerebrospinal fluid (CSF) levels of asparagine (ASN), aspartic acid (ASP), glutamine (GLN), and glutamic acid (GLU) (4) complete remission (CR), (5) minimal residual disease (MRD), (6) responder rates with respect to ASN depletion, (7) duration of ASN depletion response, (8) adverse events, (9) serum biochemistry, haematology, coagulation screen
N/A	**MC-ASP.5/ALL – Phase III (Main Study)** • *Objectives:* To demonstrate non-inferiority of recombinant L-asparaginase to asparaginase medac with regard to complete depletion of serum asparagine (i.e. to show pharmacodynamic equivalence of both preparations). • *Design:* Multicentre, randomised, active-controlled, double-blind, parallel-group study • *Administration* 5000U /m2 (I.V infusion) once every 3 days for 8 doses in 22 days of induction • *Population:* N= 199 recruited with 98 r-ASNase Medac. Children (Age ≥ 1 year and ≤ 18 years) with *de novo* T-lineage or precursor B-lineage ALL • *Endpoints:* o Primary Endpoints: Complete ASN depletion o Secondary endpoints: (1) Hypersensitivity reactions to the first dose, (2) Incidence of pre-defined asparaginase-related AEs and overall AEs, (3) Rate of complete ASN depletion in CSF, (4) Trough levels of asparaginase activity in serum, (5) Asparaginase activity levels in CSF, (6) Concentrations of amino acids ASN, ASP, GLN, and GLU in serum and CSF, (7) Trough levels of ASNase activity and ASN, ASP, GLN, and GLU levels in serum, (8) Anti-asparaginase antibodies in serum, (9) CR rate and MRD status after induction, (10) Relapse rate, relapse-free survival (RFS) and EFS at end of study

Healthy Volunteers	Affected patients

N/A	**MC-ASP.6/INF - Phase II**
	
	• *Objective:* To assess the safety and to describe the pharmacodynamics of recombinant asparaginase for first-line treatment in infants (< 1 year of age at diagnosis) with *de novo* ALL.
	• *Design:* Non-controlled multicentre, efficacy & safety study
	• *Administration:* rASNase 10,000 U/m2 once every 3 days for 6 IV infusions over 19 days
	• *Populations:* N= 12 Infants (*de novo* ALL previously untreated)
	
	• *Endpoints:*
	  • Primary Endpoint: (1) Number of pts with hypersensitivity reactions, (2) Silent inactivation of asparaginase activity
	  • Secondary Endpoint: (1) Trough level of asparaginase activity in serum (2) Concentrations of ASN, ASP, GLN, and GLU in serum (3) Number of patients with complete ASN depletion (4) Number of patients able to complete their full course of asparaginase treatment during induction (5) CR rate and MRD status after induction (6) relapse rate, relapse-free survival and event free survival at the end of the follow-up (7) anti-asparaginase antibodies

	Two additional pharmacokinetic studies in adult patients with relapsed haematological neoplasias were submitted **MC-ASP.1/ALL - Phase II (n=2 ALL) -** Open-label, non-controlled **MC-ASP.2/RHN - Phase I/II study (n= 7 NHL & AML)** - Non-controlled

Primary endpoint definition

Complete ASN depletion	Defined as ASN levels below the lower limit of quantitation (BLLQ) - ASN level ≤ 0.5 μM, for at least three of the four scheduled time points
Silent inactivation of asparaginase activity	Defined as asparaginase trough serum activity < 20 U/L (directly before recombinant asparaginase administration numbers 2, 4, and 6)

Tepadina® (Thiotepa)

Adienne S.r.l.

This is a summary of part of the CDP in support of Initial MA (17/03/2010), for acute lymphoblastic leukaemia.

The legal basis for this application refers to Article 10(a) of Directive 2001/83/EC, as amended - Well-established use application. A full bibliographical dossier containing clinical studies performed in adult and paediatric patients based on the published literature were submitted.

The below table is a summary of bibliographic studies submitted for Allogeniec HSCT in adult patient and paediatric population with leukaemia.

Age Group	Conditioning Treatment	Number of Patients	Bibliographic reference submitted
Adult	TT/CY	78	Bacigalupo et al, 1996; Bacigalupo et al, 2007c
	TT/CY/BU	30	Rosales et al, 1999
	TT/FLU/MEL/ATG	14	Lacerda et al, 2003
	TT/TBI/CY	81	Rigden et al, 1996; Papadopoulos et al, 1998
	TT/TBI/CY/ATG	107	Aversa et al, 1994; Aversa et al, 1999; Aversa et al, 2001
	TT/TBI/FLU/ATG	276	Aversa et al, 1998; Aversa et al, 2001; Aversa et al, 2002; Aversa et al, 2005
	Total	**586**	**Number of references = 12**
Children	TT/TBI/CY	97	Zecca et al, 1999 Locatelli et al, 2009
	TT/CY/ALG/TBI	41	Locatelli et al, 2009
	TT/FLU/ATG/TBI	21	
	TT/MEL/TBI	18	
	TT/FLU/TBI	19	
	TT/MEL/ALG/TBI	15	
	TT/FLU/TREO	10	
	TT/CY/ATG/TBI	8	
	Total	**228**	**Number of references = 2**

Reference Submitted (n = 14)

Aversa F. et al. (1994) Successful Engraftment of T-Cell-Depleted Haploidentical "Three-Loci'' Incompatible Transplants in Leukemia Patients by Addition of Recombinant Human Granulocyte Colony-Stimulating Factor-Mobilized Peripheral Blood Progenitor Cells to Bone Marrow Inoculum. Blood; 84: 3948-55.

Aversa F. et al. (1998) Treatment of high-risk acute l.eukemia with T-cell-depleted stem cells from related donors with one fully mismatched HLA haplotype. N Engl J Med.; 339 (17): 1186-93.

Aversa F. et al. (1999) Improved Outcome With T-Cell–Depleted Bone Marrow Transplantation for Acute Leukemia. Journal of Clinical Oncology; 17 (5): 1545.

Aversa F. et al. (2001) Haploidentical stem cell transplantation in leukemia. Blood Rev; 15: 111-19.

Aversa F. et al. (2002) Haploidentical Stem Cell Transplantation for Acute Leukemia. Int J Hematol.; 76 (Suppl 1):165-68.

Aversa F. et al. (2005) Full Haplotype-Mismatched Hematopoietic Stem-Cell Transplantation: A Phase I1 Study in Patients with Acute Leukemia at High Risk of Relapse. J Clin Oncol.; 23(15): 3447-54.

Bacigalupo et al. (1996) Thiotepa Cyclophosphamide Followed by Granulocyte Colony-Stimulating Factor Mobilized Allogeneic Peripheral Blood Cells in Adults with Advanced Leukemia. Blood; 88: 353-57.

Bacigalupo et al. (2007c) Allogeneic hematopoietic stem cell transplantation (HPCT) after conditioning with i.v. busulfan or i.v. thiotepa containing regimens. Bone Marrow Transplantation; 39 Suppl. 1: P595

Lacerda J.F. et al. (2003) Haploidentical stem cell transplantation with purified CD34 cells after a chemotherapy-alone conditioning regimen. Biol Blood Marrow Transplant; 9: 633-42

Locatelli et al. (2009) Survey of 432 patients that underwent hematopoietic progenitor cell transplantation (HPCT) in Paediatric Onco-hematological Unit of Policlinico San Matteo Hospital, Pavia, Italy.

Papadopoulos K.P. et al. (1998) High-dose thiotepa and etoposide-based regimens with autologous hematopoietic support for high-risk or recurrent CNS tumours in children and adults. Bone Marrow Transplant; 22: 661-67.

Rigden JP. et al. (1996) Minimizing graft rejection in allogeneic T cell-depleted bone marrow transplantation. Bone Marrow Transplantation; 18 (5): 913-19.

Rosales F. et al. (1999) The role of thiotepa in allogeneic stem cell transplantation in patients with leukemia. Leuk Res; 23: 947-52.

Zecca et al. (1999) Total Body Irradiation, Thiotepa, and Cyclophosphamide as a Conditioning Regimen for Children with Acute Lymphoblastic Leucemia in First or Second Remission Undergoing Bone Marrow Transplantation With HLA-Identical Siblings. J Clin Oncol 17: 1838-46.

Jylamvo® (Methotrexate Oral solution)

Therakind Limited

Jylamvo gained market access through a hybrid medicinal product application as defined in Article 10(3) of Directive 2001/83/EC. The reference product was METHOTREXAT "Lederle" 2.5mg tablets (Pfizer Corporation Austria Ges.m.b.H)

Healthy Volunteers	Affected Patients

MTX001 - BE study
 	
• *Objective:* To compare the to-be-marketed product (Jylamvo), and the reference product (Ebetrexat 10 mg tablets)
 	
• *Design:* Single-dose, open-label, laboratory blinded, randomised, two-period, two-sequenc e, cross-over
 	
• *Administration:* Oral solution (5 mL of 2mg/mL) OR 10 mg tablet PO
 	
• *Population:* 24 healthy adult subjects
 	
• *Endpoints:*
• *Primary PK Parameters*
  • Maximum observed plasma concentration (Cmax)
  • Area under the plasma concentration versus time curve (AUC) from time zero to t, where t is the time of the last quantifiable concentration (AUC(0-t))
• *Secondary PK Parameters*
  • AUC with extrapolation to infinity (AUC(0-∞))
  • Time to Cmax (tmax)
  • Percentage of the AUC0-∞ obtained by extrapolation (%AUCex)
  • Terminal elimination rate constant (λz)
  • Apparent terminal elimination half-life (t½).
	N/A

MTX002 – BE study • Objective: To compare the to-be-marketed product (Jylamvo), and the reference product (Methotrexate "Lederle" 2.5 mg tablets) • Design: single center, Single-dose, open-label, laboratory blinded, randomised, two-period, two-sequence, cross-over • Administration: Oral solution (1.25 mL of 2mg/mL) OR 2.5 mg tablet; 2.5 mg dose; Oral • Population: 24 healthy male subjects • *Endpoints:* • *Primary PK Parameters*	N/A

Healthy Volunteers	Affected Patients
• Maximum observed plasma concentration (Cmax) • Area under the plasma concentration versus time curve (AUC) from time zero to t, where t is the time of the last quantifiable concentration (AUC(0-t)) • *Secondary PK Parameters* • Cmax, syringe weight adjusted • AUC(0-t), syringe weight adjusted • Time to maximum observed plasma concentration (tmax) • Area under the plasma concentration versus time curve, with extrapolation to infinity (AUC(0-∞)) • Percentage of AUC0-∞ obtained by extrapolation (%AUCex) • Terminal elimination rate constant (λz) • Apparent terminal elimination half-life (t½) • *Safety Variables:* Hematology, Clinical chemistry, Urinalysis, Adverse events (AEs), Concomitant medication, Electrocardiogram (ECG) & Vital signs	

Xaluprine® (Mercaptopurine Oral suspension)

Nova Laboratories Ltd

Xaluprine gained market access through a hybrid medicinal product application Article 10(3) of Directive 2001/83/EC. Puri-Nethol 50 mg Tablets (GlaxoSmithkline UK)

Healthy Volunteers	Affected Patients
SC02808 - BE study • *Objective:* To evaluate the pharmacokinetic characteristics and compare the bioavailability of a Test formulation (Mercaptopurine Oral Suspension 100 mg/5 ml) and the marketed reference formulation (Puri-Nethol 50 mg Tablet • *Design:* Randomised, two-treatment, two-period, two-sequence single-dose crossover study • *Administration:* Oral solution of test product (2.5 mL of 20mg/mL) OR 50mg tablet PO Puri-Nethol (reference) • *Population:* 60 adult (mean age 23 years) healthy male volunteers • *Endpoints:* • *Primary PK Parameters:* Cmax, AUC_{0-t} and $AUC_{0\text{ -infinity}}$.	N/A

Appendix 5
List of products in phase I and phase I/II investigated in trials initiated after November 2007 separated according to drug category

Chemicals in Phase I and phase I/II			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
Everolimus (mTOR inhibitor)	Everolimus with multiagent re-induction chemotherapy	Second line	NCT01523977
5-Azacytidine (Pyrimidine analogue antimetabolite)	5-Azacytidine in combination with chemotherapy	Third line	NCT01861002
MK2206 (Akt inhibitor)	MK2206 for relapsed and/ or refractory (r/r) solid tumours or leukaemia	Second line	NCT01231919
Allopurinol (Xanthine oxidase inhibitor)	Allopurinol combined with 6MP during maintenance therapy	First line	NCT02046694
AT9283 (Selective aurora kinases inhibitor)	AT9283 for r/r acute leukaemia	Third line	EudraCT 2009-016952-36
Carfilzomib (Selective proteasome inhibitor)	Carfilzomib with combination chemotherapy for r/r ALL	Second line	EudraCT 2014-001633-84
Clofarabine (Purine nucleoside antimetabolite)	Clofarabine with combination chemotherapy for r/r ALL	Second line	EudraCT 2009-010826-20 EudraCT 2015-001174-18 EudraCT 2015-001173-41
VYXEOS (Liposomal formulation of cytarabine and daunorubicin)	Pilot Study of VYXEOS (CPX-351) for r/r hematologic malignancies.	Second line	2017-003434-87
Pinometostat - EPZ-5676 (DOT1L Inhibitor)	EPZ-5676 for r/r leukaemia with MLL gene rearrangement	Second line	NCT02141828
Fludarabine (Purine analogue antimetabolite)	Fludarabine in combination with chemotherapy with or without total body irradiation (TBI) as conditioning prior to HSCT	HSCT	NCT02446964 NCT00686556 NCT01068301

Appendix 5
List of products in phase I and phase I/II investigated in trials initiated after November 2007 separated according to drug category

Chemicals in Phase I and phase I/II			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
Forodesine (Synthetic high-affinity transition-state analogue)	PK study of oral/IV Forodesine for r/r T-ALL or B-ALL	Second line	EudraCT 2008-002219-42
Etoposide (Podophyllotoxin derivative)	Etoposide and cyclophosphamide with TBI as conditioning treatment to HSCT	HSCT	NCT00576979
MARQIBO - Liposomal Vincristine (Vinca alkaloid)	Marqibo® in Combination Induction chemotherapy for relapsed ALL	Second line	NCT02879643
Metformin (Biguanide)	Metformin in Combination with chemotherapy for relapse ALL	Second line	NCT01324180
Midostaurin (Tyrosine Kinase Inhibitor)	Oral midostaurin for MLL-rearranged ALL and AML	Second line	EudraCT 2008-006931-11
Nelarabine (Purine nucleoside antimetabolite)	Nelarabine with chemotherapy for relapse T-ALL	Second Line	EudraCT 2011-005923-42
Nilotinib (Tyrosine Kinase Inhibitor)	PK Study of Nilotinib for relapsed or imatinib resistant Ph+ CML or Ph+ ALL	Second line	NCT01077544
Nilotinib / Imatinib (Tyrosine Kinase Inhibitors)	Nilotinib and Imatinib Mesylate post HSCT in Ph+ ALL	HSCT	NCT00702403
Liquid formulation of 6MP	BE/PK study to develop a liquid formulation of 6MP	First line	EudraCT 2008-000424-86 NCT00702403
Panobinostat (histone deacetylase inhibitor)	Panobinostat for refractory hematologic malignancies	Third line	NCT01321346
Patient-individualized peptide vaccination	Patient-individualized peptide vaccination with adjuvant granulocyte-	Third line	EudraCT 2015-005281-29

Appendix 5
List of products in phase I and phase I/II investigated in trials initiated after November 2007 separated according to drug category

Chemicals in Phase I and phase I/II			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
	macrophage colony-stimulating factor (GM-CSF) for relapsed ALL		
Quizartinib (AC220) (FLT3 inhibitor)	AC220 with chemotherapy for r/r AML and ALL	Second line	NCT01411267
Ruxolitinib (JAK1/JAK2 Inhibitor	Ruxolitinib for r/r solid tumours, leukaemia, or myeloproliferative disease	Second line	NCT01164163
Selinexor (KPT-330) (Oral Selective Inhibitor of Nuclear Export (SINE))	Selinexor for relapsed childhood ALL and AML	Third line	NCT02091245
Talazoparib poly ADP ribose polymerase (PARP) inhibitor Temozolomide (alkylating agent)	Talazoparib plus temozolomide for refractory or recurrent malignancies	Third-line	NCT02116777
Temsirolimus ((mTOR inhibitor))	Temsirolimus with chemotherapy for relapsed ALL or NHL	Second line	NCT01614197 NCT01403415
Venetoclax (BCL-2 inhibitor)	Safety and PK study of Venetoclax r/r malignancies	Second line	EudraCT 2017-000439-14

Appendix 5
List of products in phase I and phase I/II investigated in trials initiated after November 2007 separated according to drug category

Advanced Therapy Medicinal Products in phase 1 or phase 1/2			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
BPX-501 T cells (CAR-T cell)	Safety of BPX-501 T cells given after HSCT	HSCT	NCT03301168
ARI-0001 cells (CAR-T cells)	Pilot study ARI-0001 cells in CD19+ relapse ALL	Second Line	EudraCT 2016-002972-29
Autologous CD19 CAR+ EGFTt + T cells (CAR-T Cells)	Trial of Genetically Modified Autologous T Cells Directed Against Relapsed CD19+ Acute Lymphoblastic Leukaemia	Second line	NCT01683279
BinD19 (CAR-T cells)	BinD19 Treatment in Childhood R/R ALL and Lymphoma Subjects	Second line	NCT03265106
CART22 cells (CAR-T Cells)	Anti-CD22 Autologous T Cells for chemo resistant or refractory ALL	Second line	NCT02650414
CD19 CAR T cells (CAR-T Cells)	T-cells Expressing Anti-CD19 CAR in Paediatric and Young Adults With B-cell Malignancies	Second line	NCT02772198
CD19/CD22 CAR-T cell (CAR-T Cells)	CD19/CD22 CAR-T cell and Chemotherapy for r/r CD19+ -ALL	Second line	NCT03241940
AUTO3 (CAR T Cells)	AUTO3 CAR T Cells for r/r CD19+ and CD22+ B-ALL	Second line	EudraCT 2016-004680-39

Appendix 5
List of products in phase I and phase I/II investigated in trials initiated after November 2007 separated according to drug category

Advanced Therapy Medicinal Products in phase I or phase I/II			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
UCART19 (CAR-T Cells)	UCART19 for r/r B ALL	Second line	EudraCT 2016-000296-24 EudraCT 2015-004293-15
Romyelocel-L (CLT-008) (Ex vivo expanded human myeloid progenitor cells)	Study of CLT-008 After Cord Blood Transplant for Haematological Malignancies	HSCT	NCT00891137
KTE-C19 (anti-CD19 CAR T cells)	KTE C19 for r/r B-ALL. ZUMA-4 trial	Second line	EudraCT 2015-005010-30
T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 (CAR T Cells)	T-Lymphocytes Genetically Targeted to the B-Cell Specific Antigen CD19 for relpased CD19+ B-ALL	Second line	NCT01860937
T cells receptor (TCR) Alfa Beta Depleted Graft (Peripheral blood stem cells)	TCR Alfa Beta Depleted Graft for ALL or AML and Receiving an HSCT	HSCT	NCT01810120

Appendix 5
List of products in phase I and phase I/II investigated in trials initiated after November 2007 separated according to drug category

Biologicals in phase I and phase I/II trials			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
Veltuzumab (anti-CD20 mAb) Epratuzumab (anti-CD22 mAb)	Study combining veltuzumab and epratuzumab with chemotherapy for recurrent B-ALL	Second line	EudraCT 2008-002286-32
Blinatumomab (bispecific T engager (BiTE) antibody)	Blinatumomab for r/r B-ALL	Second line	EudraCT 2017-003778-15
Antibody Drug Conjugates and Immunotoxins in phase I and phase II trials			
Active Substance (Drug Class)	**Trial Description**	**Line of therapy / Area**	**EudraCT Number or NTC Number**
Inotuzumab Ozogamicin (anti-CD22 antibody conjugated to calicheamicin)	Inotuzumab Ozogamicin with or without chemotherapy for r/r CD22 (+) ALL	Second line	EudraCT 2016-000227-71
DT2219ARL (Anti-CD19/CD22 bispecific ligand-directed toxin)	DT2219ARL for r/r CD19 (+), CD 22 (+) B-ALL	Second line	NCT00889408

International Pharmaceutical Federation (FIP) Presentation

Abstract accepted as a poster presentation for the 78th International Pharmaceutical Federation (FIP) World Congress of Pharmacy and Pharmaceutical Sciences, that will be held between the 2nd and 6th September 2018 in Glasgow, UK.

Pharmaceutical sciences:
Regulatory sciences
FIPSUB-2248

Emerging patterns in the clinical development of medicines in paediatric oncology

Benjamin Micallef[1], John-Joseph Borg[2], Nicolette Sammut Bartolo[1], Anthony Serracino-Inglott[1]
[1]Pharmacy, University of Malta, Msida, Malta
[2]Malta Medicines Authority, Sir Temi Żammit Buildings, Malta Life Sciences Park, San Ġwann SĠN 3000, Malta

Background: Understanding the patterns in clinical development of paediatric oncology medicinal products may facilitate the approval of safer and more effective medicines to treat children with cancer

Purpose: To review clinical development programs (CDPs) of paediatric oncology medicinal products for acute lymphoblastic leukaemia (ALL) to identify emerging patterns.

Methods: CDPs for authorised products and drugs in the development phase were retrieved from European public assessment reports, Paediatric Investigation Plans and registered clinical trials. CDPs were analysed and compared. Prospective treatment protocols were proposed based on drugs in development. The drug class and line of therapy was described for each authorised and prospective product.

Results: Nine centrally authorised products (7 small molecules and 2 biologicals) indicated to treat paediatric ALL were identified. The CDP required for authorisation varied from extensive for novel first line products, to minimal for third line products authorised under exceptional circumstance. Thirty-Five different products were described in phase II and phase III trials; 16 small molecules, 10 advanced therapies, 7 biologicals and 2 antibody drug conjugates. Liposomal delivery, pegylation and paediatric friendly dosage form development were observed in authorised and prospective products.

Conclusion: CDPs vary based on the application method chosen by companies and the indication sought. Small molecules are the most common drug class in development although new drug classes such as advance therapy medicinal products and antibody-drug conjugates are also being explored.