SeluDex

Statistical Analysis Plan

International phase I/II expansion trial of the MEK inhibitor selumetinib in combination with dexamethasone for the treatment of relapsed/refractory RAS-pathway mutated paediatric and adult Acute Lymphoblastic Leukaemia

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v1.0 Date: 24/04/18	Initial Version (Created from protocol v1.0 dated: 14/02/207)
v2.0 Date: 11/04/19	Update to Phase I OCs, clarification of PK incorporation into escalation and clarification of CRM flexible cohort size capability. DTP included in appendix. Clarification in document control sheet that the original SAP was contained in protocol v1.0.

Contents

1 INTRODUCTION

1.1 Purpose of the Statistical Analysis Plan

This Statistical Analysis Plan (SAP) provides guidelines for the analysis and presentation of results for the SeluDex trial. This plan, along with all other documents relating to the analysis of this trial, will be stored in the 'Statistical Documentation' section of the Trial Master File. The statistical analysis will be carried out by the Trial Statistician.

1.2 Summary of the Trial

Trial Design
An international, two-phase, two-group dose finding and expansion design, to include both paediatric and adult patients: phase I for dose finding; phase II for dose expansion. The trial will utilise a modified continual reassessment method (CRM) in the phase I component to determine the MTD for each group independently. The CRM is modified such that it includes a stopping rule for excess toxicity at the lowest dose level. The phase II component will expand on each of the determined MTDs, to access for evidence of activity in the patient populations. This component of the trial will be analysed using Bayesian methods, specifically, through the calculation of posterior distributions and associated probabilities for the true underlying response rates in each patient group.

Primary Objectives

Phase I

- To define the RP2D of selumetinib in combination with dexamethasone in adult and paediatric patients with relapsed/refractory, RAS pathway mutant ALL

Phase II

- To assess the preliminary anti-leukaemic activity of the combination of selumetinib at the RP2D and dexamethasone in relapsed, RAS pathway-mutant Acute lymphoblastic leukaemia (ALL) patients.

Secondary Objectives

Phase I and Phase II

- To evaluate safety and tolerability of the combination of selumetinib and dexamethasone
- To evaluate selumetinib pharmacokinetics when given in combination with dexamethasone.

Primary Outcome Measures

Phase I

- The occurrence/non-occurrence of dose limiting toxicities (DLTs) in the trial defined assessment period

Phase II

- Response to treatment at 28 days (max 35 days) as measured by morphological (complete remission (CR), complete remission with incomplete platelet recovery (CRi), partial remission (PR), Non-response (NR) (see Appendix 1 for Response Definitions)) and for patients with CNS involvement only clearance of CSF blasts. Responders will be classified on the basis of having achieved a CR or CRi.

Secondary Outcome Measures

Phase I

- The occurrence of adverse events (AEs) as measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4 and causality assessment
- Pharmacokinetic variables of selumetinib in combination with dexamethasone from the concentration time profile (area under the curve (AUC), C_{max}, T_{max}, $t_{1/2}$)

- Response to treatment as measured by response at 28 days (max 35 days) as measured by morphological (complete remission (CR), complete remission with incomplete platelet recovery (CRi), partial remission (PR), Non-response (NR) (see Appendix 1 for Response Definitions)) and for patients with CNS involvement only clearance of CSF blasts.
- Difference in pharmacokinetics of selumetinib (ΔAUC) when selumetinib is administered as single agent and in combination with dexamethasone.

Phase II

- The occurrence of AEs as measured by CTCAE version 4 and causality assessment
- The occurrence/non-occurrence of DLTs in the trial defined assessment period
- Pharmacokinetic variables of selumetinib in combination with dexamethasone from the concentration time profile (AUC, C_{max}, T_{max}, $t_{1/2}$)
- Difference in pharmacokinetics of selumetinib (ΔAUC) when selumetinib is administered as single agent and in combination with dexamethasone

Research (Exploratory) Outcomes
Exploratory pharmacodynamic (PD) biomarker studies will be undertaken if clinical responses are observed. These will include levels of phosphorylated ERK by flow cytometry in leukaemic cells from patients at several time points (cycle 1 day 1, cycle 1 day 4 and EOT visit) (Julie Irving lab, Newcastle), as well as retrospective mRNA profiling, including BIM (AstraZeneca)

Patient Population
Relapsed adult and multiple relapsed paediatric pre-B and T-ALL patients with demonstrable RAS-pathway activating mutations. Patients will be recruited from sites across the UK, as well as selected hospitals within continental Europe.

Sample Size There will be a maximum of 12 patients treated in each group in the phase I component. Once a dose has been decided upon for each group there will be a 9 patient expansion in each of these doses for phase II.

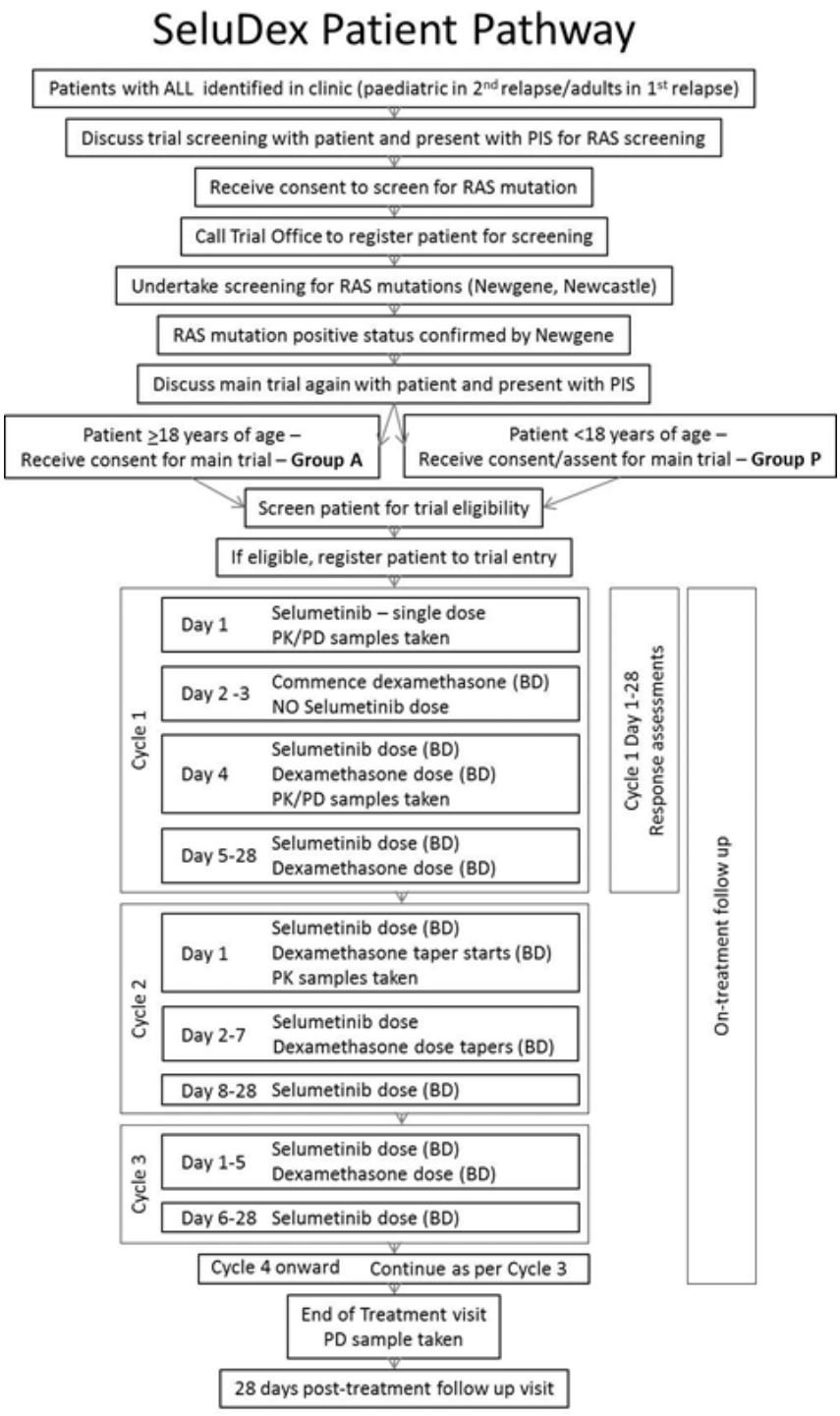
Group A (Adult)	Phase I: 12 patients	Phase II: 13 (9 + 4) patients
Group B (Paediatrics)	Phase I: 12 patients	Phase II: 13 (9 + 4) patients
Total for Phase I: max 24	**Total for Phase II: max 18**	**Total for Trial: max 42**

Table 1: Sample Size

Trial Duration
The aim is to recruit patients to both phases, into both arms of the trial over a two year period. It is anticipated that patients will be on treatment for approximately six months and will be followed up for a further month after completion of treatment.

Patient Pathway

Figure 1: Patient Pathway



2 TIMING AND REPORTING OF INTERIM AND FINAL ANALYSES

The Trial Steering Committee (TSC) will provide an oversight of the trial and provide advice through its independent chair. The TSC will review the trial data after each cohort has been recruited and followed for the DLT assessment period and the CRM model has been updated appropriately. The data presented at these reviews will consist only of the CRM dose decision data. There are no planned interim analyses for activity in the trial. The final analysis (for each group) for the dose decision phase of the trial will take place once 12 patients have been followed for the DLT assessment period, at this stage a decision will be made as to which dose to take forward to the phase II dose expansion element of the trial. The analysis for the primary outcome of the dose expansion phase (phase II) of the trial will take place once the final patient has been followed for response assessment.

An emergency meeting may be convened if a safety issue is identified or due to lack of recruitment. The TSC may consider stopping the trial early if the recruitment rate or data quality are unacceptable or there are cases of excessive toxicity that compromise patient safety. The TSC will meet or hold teleconferences at least once a year, or more often if required.

3 RECRUITMENT AND RANDOMISATION

3.1 Recruitment

The following will be reported for the recruitment:

- Date of the database snapshot used for recruitment analysis
- Total Number of patients who have been recruited into the trial
- Recruitment over time (monthly and cumulative)
- Recruitment by site/country (Choropleth)

3.2 Randomisation

There are no patient randomisations in seludex.

3.3 Ineligible Patients

Ineligible patients are defined as those registered patients who are subsequently found to not meet the eligibility criteria of the trial. The number of ineligible patients and reasons for their ineligibility will be reported; a sensitivity analysis may be conducted and reported if the number of ineligible patients is substantial. Protocol deviations relating to treatment will be reported as part of treatment compliance.

4 DATA QUALITY

Data will be collected using an electronic case report form system (eCRFs) and input into a CRCTU database. A trial specific data validation plan will be used to check for any logical discrepancies or missing data items.

4.1 Completion rate for each CRF

The number of CRFs completed will be recorded along with a percentage of that number which was expected. Any variables for which there is substantial missing data may be highlighted. Missing critical data items[1] will be explained (or at least acknowledged as queried).

[1] Critical data items as defined in CRCTU-DMA-QCD-006

4.2 Length of Patient Follow-Up

The number of alive patients lost to follow up will be reported. The median length of follow-up time from recruitment / start of treatment will also be reported.

5 TRIAL POPULATION

5.1 Baseline Patient Characteristics

A table detailing summary statistics (frequencies, percentages etc.) of baseline characteristics in all registered patients will be presented for each group. Baseline disease assessment will also be reported, including baseline toxicity.

5.2 Definitions of Populations for Analysis

Both the adult and the paediatric populations will be be analysed separately for both the phase I and phase II components of the trial. The Phase I evaluable population includes those patients who do not withdraw/die or discontinue treatment due to non-treatment related causes prior to the end of the DLT assessment period or those patients who experience a DLT.
The safety population includes all patients recruited successfully to trial who received any treatment.
The phase II evaluable population includes all patients who received any treatment.

6 TREATMENT COMPLIANCE

Analyses will report the following:

- The mean number of days dose was delayed by in those patients who experienced delays will be reported for both Selumetanib and Dexamethasone per cycle; the number of patients who experienced delays and a tabulation of reasons will also be reported.
- For both Selumetanib and Dexamethasone the number of interruptions will be reported per cycle along with the mean number of days interrupted for across patients, further to this a tabulation of reasons for interruptions will be reported.
- The mean dose received per cycle for both Selumetanib and Dexamethasone will be reported along with the number of patients who experienced a dose modification and a tabulation of the reasons for any dose modifications

7 TOXICITY AND SAFETY ANALYSIS

Toxicity and safety data will be reported for all patients which are part of the safety population defined as per 5.2.

The following details will be reported for toxicity for each group:

- Toxicities at baseline, summarised by event and number of patients experiencing such events.
- Max grade experienced for all patients.
- A summary of number of events and patients for all toxicities by event and grade.
- The number of events and patients for all grades of toxicities.
- All serious adverse events will be reported, details to be presented include; admitting event, other events, reason for SAE, outcome, sequel and relatedness.

8 ANALYSIS

8.1 Definition and Analyses of Outcome Measures

Primary Outcome Measures

The occurrence/non-occurrence of dose limiting toxicities (DLTs) in the trial defined assessment period -
The definition of a DLT is provided as follows:

DLTs will be assessed from the first dose on Cycle 1 Day 1 up until Cycle 2 Day 15 (i.e. 43 days from treatment commencement) . A DLT is defined as any toxicity which is dose limiting, is not attributable to the disease or disease-related processes under investigation, and is considered at least possibly related to either of the investigational medicinal product (IMP), as defined below:

Haematological Toxicity

- Documented bone marrow aplasia/hypoplasia, defined as overall marrow cellularity less than 25% (malignant infiltration or other causes are excluded) which does not recover by Cycle 1 Day 28. This includes an absolute neutrophil count (ANC) of less than $0.5x10^{9/L}$, and a non-transfusion dependent platelet count of less than $25x10^{9/L}$ due to bone marrow aplasia/hypoplasia
- Any Grade 5 AE
- Note: Grade 4 Febrile Neutropaenia is not a DLT

Non-haematological Toxicity

- Group P: $>$ 15% reduction in shortening fraction (SF) from baseline as measured by Echocardiogram (ECHO). Group A: Left Ventricular Ejection Fraction (LVEF) $<$ 45% on ECHO. Results must be viewed by a consultant cardiologist to confirm that there has been a genuine deterioration in cardiac function.
- Any Grade 5 AE.
- Grade 3 or 4 increased ALT or AST on or before C1D28 only which does not resolve to $\leq$ Grade 2 within 14 days (with or without supportive care)
- Grade 3 nausea or vomiting on or before C1D28 only which does not resolve to $\leq$ Grade 2 within 48 hours (with or without supportive care)
- Grade 3 mucositis which resolves to $\leq$ Grade 2 within 48 hours (with or without supportive care).
- Any other Grade 3 or 4 non-haematological toxicity, specifically excluding:
  - Alopecia
  - Dexamethasone related CTCAE grade 3 toxicities (i.e.: hyperglycaemia, muscle weakness, psychosis, avascular necrosis); note: grade 4 dexamethasone related toxicities will be considered as DLTs.
  - Tumour lysis syndrome

The Trial will utilise a modified two-stage Bayesian Continual Reassessment Method (CRM) to determine the maximum tolerated dose independently for each patient group based on the occurrence/non-occurrence of DLT. The target rate will be 0.17 (17%) for each group. The Bayesian CRM uses prior beliefs on the probability of toxicity at each dose level and the observed data to calculate a posterior estimates of the true probability of toxicity at each investigated dose level. The two-stage CRM is modified such that it incorporates stopping for excess toxicity at the lowest dose. Table 2 outlines the doses to be investigated and the prior estimates of the probability of toxicity at each investigated dose, these estimates have been elicited from clinicians. The assessment of excess toxicity at the lowest dose is made using the following criterion: The CRM will suggest to stop for excess toxicity if P($\theta_{-1} > 0.27 \mid$ Data) > 0.85, i.e. if the probability of the true rate of toxicity at the lowest dose being > 0.27 (0.1 $>$ greater than the target) is greater than 0.85. Each group has an initial design for the stage 1 component of the modified two-stage CRM (table 3). The initial designs are adhered to prior to the observance of any

Table 2: Dose Levels and Prior Estimates of Probability of Toxicity

Dose Level	Selumetanib A/P	Dexamethasone A/P	Prior probability of toxicity
-1	60mg BD PO / 20mg/m^2 BD PO	6mg/m^2/day PO divided into 2 doses	0.03
0	75mg BD PO / 25mg/m^2 BD PO	6mg/m^2/day PO divided into 2 doses	0.15
1	85-90*mg BD PO / 28-30*mg/m^2 BD PO	6mg/m^2/day PO divided into 2 doses	0.27

DLT. Once a DLT is observed the CRM will be utilised to determine the next best estimate of MTD for dose assignment. Patients are to be recruited in cohorts of 2, table 3 details the initial designs for each patient group. The CRM is capable of dealing with flexible cohort sizes should it be required. The consideration of the model determined MTD estimate for each cohort will incorporate information from the PK analysis. The TSC will incorporate these PK results into the decision process. The CRM will advise as to which doses are safe with a reported model based MTD estimate, with the PK informing if there is a need for escalation /de-escalation in contribution with the model output.

Table 3: Initial Designs for Each Patient Group

	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Cohort 5	Cohort 6
Adult Patients	Dose level 0	Dose level 0	Dose level 1	Dose level 1	Dose level 1	Dose level 1
Paediatric Patients	Dose level -1	Dose level -1	Dose level 0	Dose level 0	Dose level 1	Dose level 1

By simulating trial data under varying scenarios; different true underlying probabilities of toxicity at each dose, we are able to assess the operating characteristics of the modified CRM. Table 4 details the these scenarios and the associated operating characteristics of the design, 1000 trials were simulated under each scenario. Dose Transition Pathways for the first three cohorts for each patient group are provided in the appendix [2].

Table 4: Operating Characteristics of Modified CRM

Dose Level: A/P	60mg BD PO / 20mg/m^2 BD PO	75mg BD PO / 25mg/m^2 BD PO	85-90*mg BD PO / 28-30*mg/m^2 BD PO	Stop Trial
Scenario 1 - True toxicity rates: MTD is at dose level 1	0.02	0.05	0.17	
Probability of selection (A)	0.020	0.279	0.701	0
Probability of selection (P)	0.008	0.332	0.658	0.002
Scenario 2 - True toxicity rates: MTD is at dose level 0	0.05	0.17	0.35	
Probability of selection (A)	0.167	0.618	0.213	0.002
Probability of selection (P)	0.103	0.638	0.257	0.002
Scenario 3 - True toxicity rates: MTD is at dose level -1	0.17	0.3	0.5	
Probability of selection (A)	0.554	0.256	0.021	0.169
Probability of selection (P)	0.456	0.293	0.028	0.223
Scenario 4 - all dose levels are too toxic	0.35	0.55	0.7	
Probability of selection (A)	0.360	0.027	0	0.613
Probability of selection (P)	0.319	0.043	0.002	0.636

Response to treatment at 28 days as measured by morphological response (complete remis-

sion (CR), complete remission with incomplete platelet recovery (CRi), partial remission (PR), Non-response (NR) and for patients with CNS involvement only clearance of CSF blasts

Response will be assessed in a Bayesian framework independently for each group, with the potential for an overall assessment if response rates are found to be sufficiently similar. Responders will be classified on the basis of having achieved a CR or CRi. The trial will aim to have 13 evaluable patients in each group for the purpose of response assessment, this 13 contains those treated at the chosen MTD from the phase I component and the additional 9 from the expansion cohort. The analysis will be based on the assessment of posterior probabilities for the true underlying response rate using a minimally informative prior distribution, specifically a Beta(1,1) will be used.

A Beta distribution will be used for the prior alongside a Binomial likelihood function for our parameter of interest (true response rate) using the accumulated trial outcome data, resulting in a conjugate Beta posterior for the true underlying response rate. Posterior probabilities will be calculated for varying critical values of interest, further to this a 95% highest posterior density (HPD) interval will be presented to support any inference. The following decision rule will be implemented in SeluDex to inform our assessment of response: P(True response rate $> 0.35 \mid$ Data) > 0.80, that is, we conclude the true response rate is greater than 0.35 if the probability of true response rate being greater than 0.35 is greater than 0.8. Table 5 details the operating characteristics of such a decision rule under varying scenarios concerning the true underlying response rate.

Table 5: Operating Characteristics: Bayesian Response Assessment

True Response Rate	0.25	0.35	0.45	0.55
% of trials conclude true response rate is > 0.35 (Based on above decision rule)	8	28	58	82

The trial aims to detect an improvement in response rate from 0.35 to 0.55, from table 5 it can been seen that if the true underlying response rate is 0.55, then we have a 82% chance of correctly concluding the response rate is greater than 35% using our chosen decision rule. In 13 patients we require at least 6 patients (46%) to respond for the P(True response rate $> 0.35 \mid$ Data) > 0.80.

Secondary Outcome Measures

The occurrence of adverse events (AEs) as measured by Common Terminology Criteria for Adverse Events (CTCAE) version 4 and causality assessment

This outcome will be analysed for each group of patients independently and will report on the details outlined in section 7.

Pharmacokinetic variables of selumetinib in combination with dexamethasone from the concentration time profile (area under the curve (AUC), Cmax, Tmax, t1/2)

These pharmacokinetic variables will be reported at the patient population level for each dose level investigated using appropriate summary statistics (e.g. Mean, C.I. etc.) for each group.

Difference in pharmacokinetics of selumetinib (ΔAUC) when selumetinib is administered as single agent and in combination with dexamethasone

The difference in AUC will be measured in patients reporte both as percentage change and as absolute values, in particular this assessment of AUC will inform the dose selection for the higher (+1) dose level in the trial. Specifically investigation of the highest dose level will only take place if there is a reduction of $\geq 25\%$ in AUC seen consistently across patients. The dose of selumetinib in that case will depend on the level of reduction of selumetinib plasma concentration and will be increased linearly in relation to the AUC reduction to a maximum of 120 %

9 STATISTICAL SOFTWARE

Statistical analyses will be carried out using relevant statistical software; SAS, Stata or R respectively.

10 STORAGE AND ARCHIVING

The SeluDex database will be stored on a password protected secure SQL server. Snapshots of the database will be taken by the SeluDex Statistician for interim analyses. SeluDex files (data and reports) created are stored on a password protected user area of the secure SQL server and will be saved for archive purposes according to CRCTU policy and procedure.

11 REFERENCES

References

[1] 'Quigley, J., Pepe, M., Fisher, L. (1990). Continual Reassessment Method: A Practical Design for Phase 1 Clinical Trials in Cancer. *Biometrics*, 46(1), 33-48.

[2] Yap, C., Billingham, LJ., Cheung, YK., Craddock, C., O'Quigley, J. (2017). Dose Transition Pathways: The Missing Link Between Complex Dose-Finding Designs and Simple Decision Making. *Clinical Cancer Research*, 23(24), 7440-7

12 APPENDIX

	Dose in Cohort 1	No. DLT in Cohort 1	Dose in Cohort 2	No. DLT in Cohort 2	Dose in Cohort 3	No. DLT in Cohort 3	Dose in Cohort 4
1	2	0	3	0	3	0	3
2	2	0	3	0	3	1	3
3	2	0	3	0	3	2	2
4	2	0	3	1	2	0	2
5	2	0	3	1	2	1	1
6	2	0	3	1	2	2	1
7	2	0	3	2	1	0	1
8	2	0	3	2	1	1	1
9	2	0	3	2	1	2	1
10	2	1	1	0	1	0	2
11	2	1	1	0	1	1	1
12	2	1	1	0	1	2	1
13	2	1	1	1	1	0	1
14	2	1	1	1	1	1	1
15	2	1	1	1	1	2	
16	2	1	1	2			
17	2	1	1	2			
18	2	1	1	2			
19	2	2	1	0	1	0	1
20	2	2	1	0	1	1	1
21	2	2	1	0	1	2	
22	2	2	1	1	1	0	1
23	2	2	1	1	1	1	
24	2	2	1	1	1	2	
25	2	2	1	2			
26	2	2	1	2			
27	2	2	1	2			

Table 6: Dose transition pathways for cohorts 1-4, assuming a cohort size of 2 patients - Adult Patients

	Dose in Cohort 1	No. DLT in Cohort 1	Dose in Cohort 2	No. DLT in Cohort 2	Dose in Cohort 3	No. DLT in Cohort 3	Dose in Cohort 4
1	1	0	2	0	3	0	3
2	1	0	2	0	3	1	2
3	1	0	2	0	3	2	1
4	1	0	2	1	1	0	2
5	1	0	2	1	1	1	1
6	1	0	2	1	1	2	1
7	1	0	2	2	1	0	1
8	1	0	2	2	1	1	1
9	1	0	2	2	1	2	
10	1	1	1	0	1	0	1
11	1	1	1	0	1	1	1
12	1	1	1	0	1	2	1
13	1	1	1	1	1	0	1
14	1	1	1	1	1	1	1
15	1	1	1	1	1	2	
16	1	1	1	2			
17	1	1	1	2			
18	1	1	1	2			
19	1	2					
20	1	2					
21	1	2					
22	1	2					
23	1	2					
24	1	2					
25	1	2					
26	1	2					
27	1	2					

Table 7: Dose transition pathways for cohorts 1-4, assuming a cohort size of 3 patients. - Paediatric Patients