TOPP-2 registry

Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension

Observational Plan

Title	TOPP-2 disease registry: Tracking Outcomes and Practice in Pediatric Pulmonary Hypertension
Protocol version	V 3.0
Date of this version	18 June 2021
EU PAS register number	Not registered
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Financial disclosure	The TOPP-2 registry is supported through a research grant from Actelion Pharmaceuticals Ltd (now Janssen Pharmaceuticals Ltd)
Joint PASS	No
Objectives and research questions	1. Validate the observed changes in the variables proposed in Nice as treatment goals in pediatric pulmonary hypertension (PePH) and identify new treatment goals 2. Describe the frequency of components of clinical worsening in PePH 3. Evaluate the predictive value of these components and their composite of clinical worsening in PePH 4. Identify the current drivers of treatment strategy 5. Compare effectiveness of treatment strategies. 6. Describe disease characteristics, diagnosis and treatment in updated Nice clinical classification of PePH group 3, 4 and 5 patients 7. Characterize PAH CHD with regard to presentation, clinical course and treatment strategy, according to the proposed ABCD system
Participating countries (as of June 2021)	Australia, Brazil, Canada, China, Columbia, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Poland, Saudi Arabia, Sweden, Switzerland, The Netherlands, USA

Authors and signature

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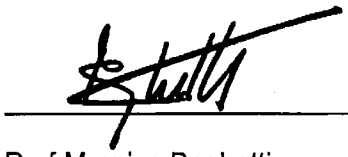
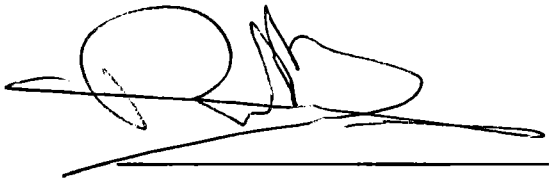


Prof Maurice Beghetti

Chairman of the PePH Executive Board



Prof Rolf Berger

Deputy chairman of the PePH Executive Board

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1 List of abbreviations

APAH-CHD	Pulmonary arterial hypertension associated with congenital heart disease
BPD	Broncho-pulmonary dysplasia
CDH	Congenital diaphragmatic hernia
CHD	Congenital heart disease
CRO	Clinical research organization
DQC	Data quality committee
EB	Executive Board (of the Association for PePH)
ECHO	Echocardiography
FC	Functional class
HC	Heart catheterization
HD	Hemodynamics
iPAH	Idiopathic pulmonary hypertension
6MWT	6-minute walk test
PAH	Pulmonary arterial hypertension
PAP	Pulmonary arterial pressure
PASS	Post-authorization safety study
PCWP	Pulmonary capillary wedge pressure
PePH	Pediatric pulmonary hypertension
PFT	Pulmonary function test
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RHC	Right heart Catheterization
WHO	World Health Organization
WSPH	World Symposium for Pulmonary Hypertension

2 Responsible parties

Sponsor

The Executive Board (EB) of the Association for PePH has designed and is responsible for TOPP-2. Members of the EB are physicians specialized in the treatment of pediatric pulmonary hypertension (PePH). As of June 2021 the EB of the Association is composed as follows:

- Maurice Beghetti, Geneva, Switzerland (chairman of Association for PePH)
- Rolf Berger, Groningen, The Netherlands
- Damien Bonnet, Paris, France
- Tilman Humpl, Lörrach, Germany
- Dunbar Ivy, Denver, USA

Financial disclosure

The Association for PePH receives a research grant for TOPP-2 from Actelion Pharmaceuticals Ltd (now Janssen Pharmaceuticals Ltd) for 6 years. Janssen is not involved in the management of, nor in the decisions related to, the registry and will not have access to the database.

The Association will provide Janssen once yearly with a report of fully anonymized, aggregated results on patient characteristics and patient medication use in the registry.

Furthermore, Janssen has the opportunity to request specific analyses that will be provided only after approval of the TOPP-2 EB. Agreement for such analyses will not be unreasonably withheld.

Scientific collaboration between the TOPP-2 investigators and Janssen employees using registry data can be initiated after agreement of the TOPP-2 EB. The content and scope of such collaboration will then be described in concert with involved parties.

3 Amendments and updates

Version	Date	Remark
V1.0	10 June 2014	Final draft
V1.1	16 June 2014	Updated after discussion between EB members and Actelion
V1.2	05 March 2015	Implementation of CRO comments Layout improvements
V1.3	20 July 2018	Protocol amendment to cover continuous enrollment, registry run-time extension and clarification on the definition of 'incident patient'
V2.0	27 July 2018	Second external version
V2.1	11 June 2021	Protocol amendment to cover early enrollment closure and runtime extension
V3.0	18 June 2021	Third external version

The Association of PePH has successfully run the international TOPP registry, which is the first registry in pediatric patients with PH to be run by the Association. For clarification, the first TOPP registry will be referred to as TOPP-1 in this document.

4 Milestones

- Q2 2015: First new incident patient included into TOPP-2
- Q2 2021: Last patient included into TOPP-2 (enrollment closure)
- Q4 2022: TOPP-2 database closure

In Q2 2015, ex-incident patients from TOPP-1 will be transferred from the TOPP-1 database into the new TOPP-2 database before inclusion of the first incident patient into TOPP-2. These patients will be further followed-up within TOPP-2, after completion of an adapted TOPP-2 inclusion CRF (for details see Section 7.4).

Once yearly data cuts and analyses are foreseen.

5 Rationale and background

The TOPP-1 global registry for pediatric PH (groups 1, 3, 4 and 5) started in January 2008. Since then, and as of June 2014, data from over 680 children with PH have been included; of those, over 50% were newly diagnosed patients. Median follow-up since inclusion is approximately 3.5 years for the total cohort and 2.5 years for incident patients. Data from TOPP-1 on patient characteristics (1), diagnostic approach (2), baseline hemodynamics (3), treatment (4), acute vasodilator response tests (5) and event rates (6) have been published. Manuscripts on outcome (solely based on incident patients) and ABCD categories are in preparation.

With TOPP-1 running for over 6 years it is imperative to consider the benefit/cost ratio of continuing the registry.

The TOPP-1 database does contain a unique and large cohort of incident PePH patients (subsequently called ex-incident TOPP-1 patients). This cohort is of great value for gaining further insights into the disease course and long-term outcome of PH in childhood. Longer patient follow-up, also in seemingly stable patients, will be required to adequately describe the frequency of events and surrogates of outcome in the different types of PePH, as well as their predictive value as components for clinical worsening in PePH.

Furthermore, during the 5th World Symposium for Pulmonary Hypertension (WSPH) in Nice 2013, the clinical classification of PH has been adapted and now includes new characterizations for children with PAH associated with congenital heart disease (CHD; ABCD-classification) and for those with group 3 PH (7). Also, current challenges in pediatric PH were defined, including the identification and validation of treatment goals, the validation of clinical worsening composites and, finally, the efficacy and safety of current and new treatment strategies in pediatric PH (8, 9).

The design of the current TOPP-1 registry developed in 2007 does not, however, allow answers to the questions outlined above, either because variables were not specified in 2007 (e.g. ABCD-classification for PAH-CHD, neonatal history in PH associated with pulmonary developmental conditions, e.g. broncho-pulmonary dysplasia [BPD]) or because diagnostics and follow-up investigations vary between centers and patients, and are incompletely captured in the current registry. Also, data to identify treatment strategies are not adequately captured. These restrictions limit the use of the TOPP-1 database to address current challenges in the care for children with PH (10).

Therefore, a new TOPP-2 registry has been designed, using the updated definitions and classification as proposed at the WSPH 2013 in Nice and recruiting only from sites that declare to be committed to follow, in their daily clinical practice, the new pediatric diagnostic and follow-up guidelines as proposed at the WSPH 2013 (8). Only these sites will participate in TOPP-2. The data collection form for TOPP-2 will reflect the new clinical classification (7) and diagnostic

criteria (8). The TOPP-2 follow up CRF is specifically designed to capture the variables that have been proposed as treatment goals in PePH and to capture reasons for changes in treatment strategy.

6 Objectives and research questions

The TOPP-2 registry aims to:

1. Validate the observed changes in the variables proposed in Nice as treatment goals in PePH (see Ivy et al. 2013, Table 4 (8)) and identify new treatment goals
2. Describe the frequency of components of clinical worsening in PePH
3. Evaluate the predictive value of these components and their composite of clinical worsening in PePH
4. Identify the current drivers of treatment strategy
5. Compare the effectiveness of treatment strategies
6. Describe disease characteristics, diagnosis, treatment and outcome in updated Nice clinical classification of PePH group 3, 4 and 5 patients
7. Characterize PAH-CHD with regard to presentation, clinical course and treatment strategy, according to the proposed ABCD system

7 Research methods

7.1 Registry design

TOPP-2 is an international, prospective observational registry collecting data on children and adolescents consecutively diagnosed with PH. Patients undergo clinical assessments and receive standard medical care, as determined by the patient's physician in centers that have declared to be committed to follow the pediatric diagnostic and follow-up guidelines, as proposed at the WSPH 2013, in their daily clinical practice. Patients do not receive (experimental) intervention or treatment as a consequence of their participation in the registry.

As this is a real-world, observational, non-interventional study design, the frequency of visits is determined by the physician and by the health care needs of the patient. Nevertheless, participating sites have declared to adhere to the guidelines, proposed by the Pediatric Taskforce at the WSPH Nice, emphasizing the importance of continuous repeat evaluation of progression of disease in children with PH (8). Consistent with standard care, physicians are encouraged to schedule patient visits at least once a year. All visits will be documented in the registry.

7.2 Timelines

The TOPP-2 registry is a long-term project. TOPP-2 is scheduled to be up and running, i.e. patients from TOPP-1 migrated and first patient included, in Q2 2015.

The inclusion period will run until 30 June 2021. Registry closure is scheduled for 31 December 2022, i.e. all patients will have at least 18 months of follow-up. Per 18 June 2021, 383 patients were enrolled into the TOPP-2 registry; approximately 385 patients are expected to be enrolled until enrollment closure.

7.3 Setting

7.3.1 Participating sites

Sites from all over the world, following the diagnostic work-up and follow up monitoring as proposed by the WSPH Pediatric Taskforce in Nice 2013 (8), are eligible for participation in TOPP-2. Some sites from the ongoing TOPP-1 registry might not be eligible for TOPP-2, either due to underperformance[1] in the TOPP-1 registry, or non-commitment to the new guidelines[2].

Initiated countries, as of June 2021, are Australia, Brazil, Canada, China, Columbia, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Poland, Saudi Arabia, Sweden, Switzerland, The Netherlands and USA.

7.3.2 Inclusion criteria for sites to participate in TOPP-2

A declaration of the site's commitment to the Nice guidelines and performance criteria will be included in the participant agreement, which must be signed by all sites participating in TOPP-2.

7.3.3 Patient population

The patient population documented in TOPP-2 will include:

- Ex-incident TOPP-1 patients, meeting all inclusion criteria according to TOPP-1 and who agree to continue their registry participation by signing the TOPP-2 informed consent form upon inclusion of sites who participated in TOPP-1 for inclusion in TOPP-2
- Children and adolescents, newly diagnosed with PH (incident PePH patients), meeting the inclusion criteria as listed below. A patient is considered an incident patient if the time elapsed between the diagnostic RHC and the initial visit at the site including the patient is less than or equal to three months **and** if the time between diagnostic RHC and informed consent is less than or equal to 6 months

In order to accurately capture the target population and to minimize the potential for selection bias, all participating sites should screen and evaluate for possible inclusion all consecutive patients that present at their site and are diagnosed with PH. Consecutive patients who meet the eligibility criteria should be informed about the registry and given the opportunity to provide informed consent, i.e. written informed consent either by themselves and/or their legal guardians.

Ex-prevalent patients from TOPP-1, as well as incident patients who did not meet all inclusion criteria and who are therefore not included in the PH-confirmed patient population, will not be further followed up in TOPP-2, nor will be patients from TOPP-1 sites who will not participate in TOPP-2.

7.3.4 Inclusion criteria for new incident patients included into TOPP-2

The following qualifications must be met by patients for their data to be entered into TOPP-2. Differences to inclusion criteria for TOPP-1 are indicated in the relevant footnotes.

- Patient must be an incident patient, i.e. newly diagnosed with PH (see above)
- Age at time of diagnosis $\geq$ 3 months and < 18 years old[3]

[1] Defined as a) non- or little follow-up documentation in TOPP-1, and/or b) unresponsiveness to queries and/or c) unsatisfactory data quality (high percentage of patients not meeting inclusion criteria in TOPP-1)

[2] Sites contacted for participation will have to declare adherence to the Nice guidelines and fill in a feasibility questionnaire, testing this adherence

[3] Up to the 18th birthday

- Patients must present with PH belonging to one of the following categories[4]:
  - Group 1 according to updated Nice clinical classification
  - Group 3 according to updated Nice clinical classification
  - Group 4 according to updated Nice clinical classification
  - Group 5 according to updated Nice clinical classification

Patients belonging to group 2 are not eligible for inclusion into TOPP-2.

- PH must be confirmed by heart catheterization (HC)[5]
- At HC, the patient should present with:
  - PAP mean ≥ 25 mmHg at rest
  - PVRi ≥ 3 Wood Units × m^2
  - PAWP mean ≤ 15 mmHg[6]
- In case of CHD patients who had undergone palliative procedure or repair to close systemic to pulmonary shunt, the diagnosis of PH must have been confirmed by HC at least 6 months[7] after surgery/palliative procedure took place.
- Patients to be included into the registry, and/or their legal guardians, must give informed consent. Where applicable patients will be asked for their written assent.

Sites should only include patients who are close to adult age, or referred to them from other sites for diagnosis, if the site anticipates to be able to document (at least one) follow-up visit per year.

7.4 Collected data and variables

Data collected at time of inclusion of newly diagnosed patients included in TOPP-2

At time of inclusion into the registry, data on prior medical history and on the current clinical status will be collected. Data entered will include:

- Demographics
- Etiology
- Disease characteristics
- Medical history
- Concomitant diseases
- PH symptoms and clinical status at diagnosis
- Sexual maturation
- Diagnostic work up
- Treatment

Data newly collected for ex-incident TOPP-1 patients before first follow-up visit within TOPP-2 can be documented

- For group 1 patients with CHD: ABCD classification[8]

[4] Previous (WHO) clinical classification was used for TOPP-1 (Venice)

[5] Confirmation of diagnosis by ECHO, approved by EB, was accepted for inclusion into TOPP-1

[6] For TOPP-1: PAWP mean ≤ 12 mmHg

[7] In TOPP-1, diagnosis of PH had to be confirmed by HC at least 1 year after intervention

[8] Eisenmenger vs. left to right shunt vs. PAH with co-incidental CHD vs. post-operative PAH vs. “cannot be classified” (7,8)

- For group 3 patients: Questions related to developmental lung disease not covered in CRF of TOPP-1[9]

Data collected during follow-up

- Follow up variables, as proposed by pediatric task force, WSPH Nice 2013
- Clinical status including functional class (WHO and Panama (11)) and PH symptoms
- Sexual maturation and growth
- Laboratory tests, ECHO, 6MWT, PFT, RHC
- Treatment and reasons for treatment changes
- Hospitalizations and adverse events

Discontinuation of data collection

In case data collection is terminated for any one patient, the reason for and date of termination of data collection is recorded. In case data collection is terminated due to death of the patient, reason for and date of death is collected. In case of transplanted patients, transplantation type and date of transplantation is collected.

Variables

Outcome variables may vary with the different objectives of the registry.

7.4.1 Aim 1: Treatment goals

Validate the proposed Nice treatment goals in PePH and identify new treatment goals.

7.4.1.1 Outcome variables

Primary outcome variables

- Death
- Transplantation

Secondary outcome variables

- PAH related hospitalization
- Use/initiation of iv/sc prostanoids
- Atrial septostomy
- Potts shunt
- Time to clinical worsening (various composites of above parameters)

Co-variables

- Progression/regression of symptoms
- Presence/absence of syncope
- Growth
- Change in functional class
- Change in BNP/NT-proBNP
- Changes in echocardiographic variables (TAPSE, RV/LV dimension ratio)

[9] See CRF sections 3.2.6 (including ACD with misalignment of veins, lung hypoplasia, surfactant protein abnormalities, pulmonary interstitial glycogenosis, pulmonary alveolar proteinosis, pulmonary lymphangiectasis) and 4.2 (neonatal history)

- Change in hemodynamic parameters
- Demographics, patient characteristics

7.4.2 Aim 2: Frequency of surrogates

Describe the frequency of surrogates of outcome in PePH.

7.4.3 Aim 3: Value of surrogates

Describe the predictive value of surrogates proposed as component of clinical worsening in PePH.

Descriptive and survival analysis.

Outcome

- Death
- Transplantation

Surrogate outcomes

- PAH related hospitalization
- Initiation of iv/sc prostanoids
- Atrial septostomy, Potts shunt
- Symptoms
- Decline in 6MWT, functional class, worsening of ECHO, increase in BNP/NT-proBNP
- Time to clinical worsening (various composites of above parameters)

Co-variables

- Patient characteristics

7.4.4 Aim 4: Treatment strategy

Identify the current drivers of treatment strategy.

Descriptive.

Outcome

- Type of treatment (drug, mono/combination, administration route)
- Switch in treatment
- Escalation of treatment
- Reason for treatment changes

Co-variables

- Patient characteristics, demographics, clinical variables, incl. functional class, laboratory variables, echocardiographic variables

7.4.5 Aim 5: Treatment strategy and outcomes

Analyze associations between treatment strategies and outcomes in terms of safety as well as efficacy.

Outcome efficacy and safety

- Death
- Transplantation
- Adverse events (elevated transaminases etc.)

Co-variables

- "Propensity score"
- Type of treatment
- Switch in treatment
- Escalation of treatment
- Patient characteristics

7.4.6 Aim 6: PePH group 3 patients

Describe diagnosis, disease characteristics, treatment and outcome in updated Nice clinical classification of PePH group 3 patients.

7.4.7 Aim 7: PAH-CHD

Characterize PAH-CHD with regard to presentation, clinical course and treatment strategy, according to the proposed ABCD system.

Descriptive Variables

- Demographics
  - Age at diagnosis
  - Gender
  - Ethnicity
- Etiology, diagnostic classifications
- Disease-specific characteristics
- Co-morbidities (including genetics, syndromes)
- Functional class (NYHA, Panama (11))
- 6MWD, exercise capacity
- Biomarkers
- ECHO variables
- Hemodynamic variables
- Treatment strategies
- Outcome: death, transplantation

7.5 Data sources

The patient medical records will be the main data source for data entered into TOPP-2. Data collected are data from assessments routinely performed for PH patients in clinical practice.

If measurement of any of the variables does not occur in the normal course of patient care, clinical practice should not be changed in any way just to accommodate collection of additional data.

7.6 Study size

The registry initially aimed to enroll approximately 60 patients per year for 3 consecutive years. To prevent overrepresentation of patients with PAH-CHD from specific sites or overall, the protocol pre-specifies that enrollment of CHD patients can be stopped by the EB of the Association for PePH, either at a site or overall, should the number of CHD patients included surpass 50% of the targeted patients. Also, to maximize global generalizability, it is at the discretion of the EB to close down a site, should performance be sub-optimal, or should the rate of inclusion lead to a potential bias, i.e. overrepresentation of a country.

Sample size calculations have been made based on the following assumptions and definitions:

- A minimum of 60 incident PePH patients will be included into TOPP-2 per year (estimate based on TOPP-1 experience)
- TOPP-1 ex-incident patients are included in TOPP-2 following collection of new baseline information, allowing for 10% loss due to sites not selected for TOPP-2. The final composition of TOPP-2 will be approximately 56% ex-incident and 44% incident patients (see Table 1 below)
- Calculations assume comparison of a 'binary' outcome: "exposed patients" vs. "unexposed patients". Exposed can mean, e.g. high level of biomarker, etiology classification or certain treatment group
- The statistical analysis is assumed to be a time-to-event analysis, and the relevant survival estimates are taken from previous analyses of the TOPP-1 cohort. The effect size reported below is therefore a hazard ratio

Table 1: Estimated number of ex-incident and incident patients in TOPP-2

	Date	**Oct-15**	**Oct-16**	**Oct-17**	**Oct-18**	**Oct-19**	**Oct-20**
		Year 1	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**
TOPP-1 ex-incident	Patients	246	234	222	211	200	190
	Loss to follow-up		12	12	11	11	10
TOPP-2 incident	Patients	60	117	171	162	154	146
	Loss to follow-up		3	6	9	8	8
Total	Total patients	306	351	393	373	354	336
	Person years	153	482	854	1238	1602	1947

Table 2 (for death) and Table 3 (for clinical worsening 2) summarize the effect sizes required to detect with 80% power a difference between the exposed and unexposed group, assuming 3 years of inclusion, followed by a minimum of 3 years follow-up for all patients.

Table 2: Effect sizes required to detect a difference in death between exposed and unexposed patients

Death – all cause	**Effect size detected at 80% power, 5% significance level**		
	Year 4	**Year 5**	**Year 6**
10% exposed	0.34	0.35	0.35
20% exposed	0.43	0.44	0.44
30% exposed	0.46	0.47	0.47

As an example, for "death": If 30% of the patients are exposed (e.g. to a certain treatment strategy), this will allow with 80% power to detect a relative risk (hazard ratio) of death of 0.47, i.e. the risk in the exposed group is 47% of the risk in the non-exposed group in the 6th year of the registry (including the three year inclusion period). For risk factors where only 10% are exposed, the effect would have to be larger (0.35 vs. 0.47) to be declared significant at the same 80% power.

Table 3: Effect sizes required to detect a difference in clinical worsening 2 between exposed and unexposed patients

Clinical worsening 2*	Effect size detected at 80% power, 5% significance level		
	Year 4	Year 5	Year 6
10% exposed	0.57	0.60	0.63
20% exposed	0.64	0.66	0.69
30% exposed	0.67	0.69	0.71

*Clinical worsening 2 is defined as death (all cause), transplantation, PAH related hospitalization, atrial septostomy, "deterioration of WHO functional class", initiation of iv/sc prostanoids and syncope

As an example, for "clinical worsening 2": If 30% of the patients are exposed (e.g. to a certain treatment strategy), this will allow with 80% power to detect a relative risk (hazard ratio) of clinical worsening of 0.71, i.e. the risk in the exposed group is 71% of the risk in the non-exposed group in the 6th year of the registry (including the three year inclusion period).

The sample size requirements for survival analysis are quite similar at year 5 and year 6 of the cohort. However, the additional follow-up and accumulation of almost 700 additional person years of exposure, is considered to be essential to observe both safety outcomes, and sufficient treatment changes to address aims 4 and 5. In addition, the accumulation of outcome events adds power to the event rate analyses.

TOPP-2 met its initial enrollment goal of 200 patients in September 2017. To further support the power of the registry, enrollment will remain open until 30 June 2021, i.e. 18 months prior to registry closure, which is scheduled for 31 December 2022. Per 18 June 2021, 383 patients were enrolled into the TOPP-2 registry. Approximately 385 patients are expected to be enrolled until enrollment closure.

7.7 Data management

7.7.1 Data entry

A state of the art web-based electronic data capture (EDC) system is used for data entry.

7.7.2 Data access and security

Access to the patient database will be restricted to authorized users, who will authenticate themselves with a unique combination of User ID and password.

In order to guarantee the anonymity of the patient data within TOPP-2, no names, initials or date of birth are stored within the system. When setting up a patient the site enters initials, date of birth and gender for the system to generate a unique patient identifier. Immediately thereafter, initials and day of birth are deleted from the database and can no longer be retrieved. A document describing the process is available on request.

An audit trail is maintained by the EDC system for all data entries and changes. This trail will indicate what the entries/changes have been, who has made them and when.

An https:// connection will be used for secure data transfer. Data will be encrypted when transferred over the internet and will be stored in a secure database protected from unauthorized access.

7.7.3 Responsibility for data entry

The first site including a patient into the registry is responsible for data entry for this patient. Should for any reason another site try to include the same patient, the system will recognize this based on the mechanism of generating the patient ID and will trigger a message, informing the site that the patient has already been included and by which site.

Transfer of data entry responsibility for a patient from one site to another is possible if both sites agree. Such data transfer requires manager rights and will be executed by the company hosting the data or the Clinical Research Organization (CRO).

7.7.4 Data ownership

The individual sites own the data entered from their patients. Consolidated data from all participating sites are the property of the Association for PePH.

7.8 Analyses plan

The primary analysis set will be the newly diagnosed, incident patients with PH enrolled in the TOPP-2 registry together with the ex-incident patients migrated from the TOPP-1 registry. As these two patient sets each comprise approximately half the total patient population, there is scope to conduct secondary sensitivity analysis restricted to each patient set, in particular to investigate the potential impact of survival bias in the ex-incident TOPP-1 patients.

Table 4 depicts the objectives of the TOPP-2 registry and the foreseen statistical approach.

Table 4: Objectives and statistical approach as foreseen in the analysis plan

Objective	Foreseen statistical approach
1. Validate the observed changes in the variables proposed in Nice as treatment goals in PePH and identify new treatment goals	Survival analyses and event rates using treatment induced changes as 'exposure' and primary and secondary clinical outcomes
2. Describe frequency of components of clinical worsening in PePH	Descriptive analyses
3. Evaluate the predictive value of these components and their composite of clinical worsening in PePH	Survival analyses and event rates using components as 'exposure' and primary clinical outcomes
4. What are the current drivers of treatment strategy?	Correlation analysis of change in therapy against changes in the markers. Survival analyses using time-dependent clinical worsening surrogates as outcomes and patient covariates as 'exposure'
5. Compare effectiveness of treatment strategies	Survival analyses and event rates; “propensity score” analyses.
6. Describe disease characteristics, diagnosis, treatment and outcome in updated Nice classification of Pediatric PH group 3, 4 and 5 patients	Descriptive analyses
7. Characterize PAH-CHD with regard to presentation, clinical course and treatment strategy, according to the proposed ABCD system	Descriptive analyses and survival analyses of outcome using ABCD classification as 'exposure'

Objectives 2, 4, 6 and 7 will be partly addressed by detailed descriptive analyses of the accumulated data, including characterizing the disease characteristics, diagnosis, treatment and clinical course of selected etiological groups. For these analyses, standard numerical summaries including proportions/percentages, or mean/median and appropriate measures of spread will be produced in tabulated form within relevant subgroup classifications. For description of survival, KM survival estimates will be used.

Objectives 1, 3, 4 and 7 will be addressed by event rates analysis and survival analysis. Person time will be measured as time from diagnosis/enrollment to end of follow-up and summed over patient subgroups. Event rates will be enumerated for the outcome variables listed in section 7.4, either as first event, using person-years follow-up curtailed at the event, or as all events by counting the person years for the full course of follow-up. Event rate estimates will be presented with confidence intervals based on a normal approximation, or when number of events is small using the exact Poisson distribution.

For survival analysis, Kaplan-Meier survival estimates accounting for censoring will be tabulated for 6-month follow-up intervals. Multivariable assessment of outcomes by the co-variables defined in section 7.4 will be conducted using Cox proportional hazard models, with a blocked stepwise selection of variables to determine a final model of significant predictive co-variables after adjustment.

For objective 3, in order to provide a framework to forecast post-diagnosis survival for an individual patient, a risk prediction equation will be developed using the predicted survival estimates from the Cox proportional hazards model, similar to methods previously reported by Humbert et al. (12). Using this approach, baseline survival is estimated via a weighted non-linear regression model and predictions obtained by incorporating co-variable estimates in an equation to predict survival.

For objective 5, the propensity score approach will be used to compare treatment success outcomes among non-randomized subgroups that define alternative treatment strategies (mono-, duo-, triple-therapy, time-dependent; iv therapy etc.). In this approach, a propensity score model is developed using the co-variables to establish the probability of exposure to a specific treatment conditional on observed variables. Patients are then randomly sorted and matched to the most similar patient in the comparison treatment group, in order to remove imbalances in the measured covariates. Similarity is determined by nearest neighbor algorithms (using all covariates). Random effects model can be used to model the treatment effect allowing for the matching.

7.9 Quality control

The use of EDC will allow for on-line data quality checks, i.e. edit/range checks upon data entry. Values entered which are outside of the predefined ranges, will be marked as implausible in the database. In order to ensure consistent completion of the CRF across sites, a CRF completion guide will be built into the eCRF system, including relevant definitions.

The EDC system will block documentation of patients not meeting the inclusion criteria.

EB members will act as members of the Data Quality Committee (DQC). The purpose of the DQC is to assure data quality within the TOPP-2 registry. In particular they will review the registry data for patient inclusion and for plausibility of HD data entered.

To ensure data confidentiality, the DQC will be blinded to the origin of the data, i.e. to the identity of the site. To ensure confidentiality sites will be identified by a number. The real identity will be known to the CRO and/or the project manager only. Results of assessments of the DQC, and if appropriate inquiries or recommendations, will be provided in written form to the CRO/project manager. The CRO/project manager will follow-up with the respective site without disclosing the identity to the DQC without the agreement of the site concerned. In case of serious performance issues, the DQC retains, however, the right to request identification of the site.

The DQC will not get access to individual patient data of other sites, except for the echocardiographic data in order to decide on the inclusion of patients for whom no HC has been done. In these cases the DQC will also know the origin of the data, i.e. the site.

In addition, staff from the CRO, or the project manager, might review the data for missing data points and incomplete or inconsistent information that can result in queries. However, registry data are not verified against source documents.

7.10 Limitations of the research methods

Treatments received by pediatric PH patients at the time of inclusion into the registry and throughout the registry are not directed in any way by the registry protocol. Rather, all measurements, interventions and treatments are under the direction of the treating physician. Thus, any comparisons between treatments will take into account potential confounding factors such as differences in patient characteristics, which may exist between treatment groups.

Therapy assessment may also be biased by the approval and reimbursement policies for medications of the different countries.

Participating sites have declared that they are committed to the guidelines proposed by the pediatric task force at the WSPH, Nice 2013.

To minimize the potential for selection bias, all sites are asked to evaluate for inclusion all consecutive patients diagnosed with PH, and to seek informed consent from all eligible patients.

The DQC retains the right to stop inclusion of patients at any site should the number of patients or quality of the data threaten the validity of the registry or lead to potential bias.

8 Protection of human subjects

The TOPP-2 registry does not involve any investigational or interventional procedures, which are not part of the normal clinical practice at any of the participating sites. Participation in the registry does not affect medical care. Data collected are kept strictly confidential (see section data access and security). Patients are at any one time free to withdraw their consent without giving any reason.

9 Management and reporting of adverse events/adverse reactions

This registry is made possible through a research grant from Actelion Pharmaceuticals Ltd (now Janssen Pharmaceuticals), marketing authorization holder for products used to treat PH. Patients included in TOPP-2 might be treated with these products.

To make sure Janssen can comply with its worldwide pharmacovigilance regulatory obligations, the Association has a system in place for its CRO to identify and follow-up potentially reportable adverse events for Janssen's products of which the Association becomes aware through the TOPP-2 registry.

10 Plans for disseminating and communicating study results

It is currently envisaged to do and analyze yearly data cuts. Results will be presented at specialized congresses and published in peer-review journals.

Participating sites will have on-line access to reports describing/summarizing the data from their site.

For the publication policy see Annex 1 to this protocol.

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Annex 1: Publication policy

The Association for PePH (Association) will, in accordance with standard editorial and ethical practice, support and drive publications and presentations based on the TOPP-2 registry data. As the TOPP-2 registry is a multi-center project, the Executive Board of the Association (thereafter called "Board") has established a uniform procedure for the publication and dissemination of results from this registry.

The members of the Board of the Association will drive and author, on behalf of all TOPP-2 investigators, the publications on the main registry objectives. All TOPP-2 investigators will be listed, if this is accepted by the journal to which the manuscript is submitted. In addition, the Board will invite TOPP-2 investigators to be among the main authors of the publication. Such invitation will be made based on the contribution of the site to TOPP-2 and authorship criteria[10]. As a minimum condition co-authors must actively participate themselves in the TOPP-2 registry, do a quality diagnostic work up of all patients included, have follow-up documented for their patients and take part in writing or reviewing the manuscript.

All sites participating in TOPP-2 are encouraged to use the TOPP-2 database to ask research questions and to publish on data generated within the TOPP-2 registry. This includes publications on topics driven by the Board, once the first manuscript on such a topic has been accepted for publication, or twelve (12) months after closure of the TOPP-2 registry, whichever occurs first.

For manuscripts based on multi-center registry results, the site shall furnish the Board with a copy of any proposed publication at least thirty (30) days in advance of the proposed submission date or disclosure to a 3rd party. The Board shall review the proposed publication within 30 days and shall inform the site in writing of any objection to inclusion of specific content in the proposed publication. Upon receiving the written objection from the Board, the investigator shall edit the proposed publication to remove the objectionable information before submission. The physician driving the publication will be its first author. All manuscripts on multi-center data will be co-authored by at least one of the Board members. The order of the co-authors will be agreed among contributors according to scientific contribution. In case of disagreement, the Board will make the final decision.

The Board does not foresee the publication of any results based on data from one site only. Should sites wish to publish site-specific results, the responsibility for the analyses and for writing the manuscript lies with the respective site.

The TOPP-2 registry is supported by a research grant from Actelion Pharmaceuticals Ltd. (now Janssen Pharmaceuticals Ltd). As acknowledgment of this support, the Association has agreed to furnish Janssen any draft publication in connection with the TOPP-2 registry for preview and comments at least 30 days prior to planned submission of the manuscript. Janssen's financial support will be acknowledged in all publications and presentations based on TOPP-2.

[10] See: Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication (ICMJE); Updated October 2004, International Committee of Medical Journal Editors.

Annex 2: Amendments

Amendment 1

Executive summary (page 1)

Old text

Not applicable

New text

Clinicaltrials number NCT 02610660

Rationale for change

The clinicaltrials number was added in the interest of completeness.

Executive summary (page 1)

Old text

Participating countries (in progress) Countries considered for participation include Argentina, Australia, Bolivia, Brazil, Canada, China, Colombia, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Jerusalem, Mexico, Poland, Saudi Arabia, South Africa, Spain, Sweden, Switzerland, the Netherlands, Turkey, UK and USA.

New text

Participating countries (as of July 2018) Australia, Brazil, Canada, China, Columbia, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Poland, Saudi Arabia, Sweden, Switzerland, The Netherlands, USA.

Rationale for change

The country list was updated according to current participating sites.

2. Responsible parties (page 6)

Old text

- Dunbar Ivy, Denver, USA (chairman of Association for PePH)
- Rolf Berger, Groningen, The Netherlands
- Damien Bonnet, Paris, France
- Maurice Beghetti, Geneva, Switzerland
- Tilman Humpl, Bern, Switzerland

New text

- Damien Bonnet, Paris, France (chairman of Association for PePH)
- Maurice Beghetti, Geneva, Switzerland
- Rolf Berger, Groningen, The Netherlands
- Tilman Humpl, Bern, Switzerland
- Dunbar Ivy, Denver, USA

Rationale for change

The board member list was updated according to the current status.

3. Amendments and updates (page 6)

Old text

The Association of PePH is currently (as of March 2015) successfully running the international TOPP registry, which is the first registry in pediatric patients with PH to be run by the Association. For clarification, the first TOPP registry will be referred to as TOPP-1 in this document.

New text

The Association of PePH has successfully run the international TOPP registry, which is the first registry in pediatric patients with PH to be run by the Association. For clarification, the first TOPP registry will be referred to as TOPP-1 in this document.

Rationale for change

The closure of TOPP-1 has been document in consideration of the current status.

4. Milestones (page 7)

Old text

- Q2 2015: First new incident patient included into TOPP-2
- Q4 2021: Last patient included into TOPP-2 and TOPP-2 database closure

New text

The Association of PePH has successfully run the international TOPP registry, which is the first registry in pediatric patients with PH to be run by the Association. For clarification, the first TOPP registry will be referred to as TOPP-1 in this document.

Rationale for change

The TOPP-2 registry is one of the largest databases in pediatric PH collecting observational data based on a global site distribution. Extending the registry run-time until 31 December 2018 and enrollment until registry closure will allow data analysis to be based on a larger patient number and support the explanatory power of results with an already established registry study infrastructure.

4. Rationale and background (page 7)

Old text

First data from TOPP-1 on patient characteristics and diagnostic approach have been published. One manuscript on baseline hemodynamics and one on treatment are ready for submission. One manuscript on outcome (solely based on incident patients) and one on acute vasodilator response tests are in preparation. Further analyses on gender differences and on the prognostic value of the biomarkers NT-proBNP and BNP are in progress.

New text

Data from TOPP-1 on patient characteristics, diagnostic approach, baseline hemodynamics, treatment and acute vasodilator response tests have been published. Manuscripts on outcome (solely based on incident patients) and ABCD categories are in preparation.

Rationale for change

The TOPP-1 publications have been updated to reflect the current status.

7.2 Timelines (page 8)

Old text

The TOPP-2 registry is a long-term project. TOPP-2 is scheduled to be up and running, i.e. patients from TOPP-1 migrated and first patient included, in Q2 2015.

The inclusion period will run for up to 3 years, allowing the inclusion of approximately 200 patients. All patients included will have a minimum follow-up of 3 years.

New text

The inclusion period will run until registry closure. Registry closure is scheduled for 31 December 2021. Per 27 July 2018 247 patients were enrolled into the TOPP-2 registry. Approximately 440 patients are expected to be enrolled until registry closure.

Rationale for change

The inclusion period was updated to reflect the extended enrollment and registry run-time (see rationale for 4. Milestones).

7.3.1 Participating sites (page 9)

Old text

Countries considered for participation include Argentina, Australia, Bolivia, Brazil, Canada, China, Colombia, Denmark, Finland, France, Germany, Hungary, Italy, Japan, Jerusalem, Mexico, Poland, Saudi-Arabia, South Africa, Spain, Sweden, Switzerland, the Netherlands, Turkey, UK and USA.

New text

Initiated countries, as of July 2018, are Australia, Brazil, Canada, China, Columbia, France, Germany, Hungary, Israel, Italy, Japan, Mexico, Poland, Saudi Arabia, Sweden, Switzerland, The Netherlands and USA.

Rationale for change

The country list was updated according to current participating sites.

7.3.3 Patient population (page 9)

Old text

Children and adolescents, newly diagnosed with PH (incident PePH patients), meeting the inclusion criteria as listed below. A patient is considered an incident patient if the time elapsed between the diagnostic RHC and the initial visit at the site including the patient is less than or equal to three months

New text

Children and adolescents, newly diagnosed with PH (incident PePH patients), meeting the inclusion criteria as listed below. A patient is considered an incident patient if the time elapsed between the diagnostic RHC and the initial visit at the site including the patient is less than or equal to three months **and** if the time between diagnostic RHC and informed consent is less than or equal to 6 months.

Rationale for change

The definition of incident patients was updated to implement a maximum timeline for diagnosis to ensure recently diagnosed patients are enrolled.

7.6 Study size (page 13f)

Old text

The registry aims to enroll approximately 60 patients per year for 3 consecutive years.

New text

The registry aimed to enroll approximately 60 patients per year for 3 consecutive years.

TOPP-2 met its initial enrollment goal of 200 patients in September 2017. To further support the power of the registry, enrollment will remain open until registry closure, which is scheduled for 31 December 2018. Per 27 July 2018 247 patients were enrolled into the TOPP-2 registry. Approximately 440 patients are expected to be enrolled until registry closure.

Rationale for change

The study size was updated to reflect the extended enrollment and registry run-time (see rationale for 4. Milestones).

Amendment 2

Executive summary (page 1)

Old text

The TOPP-2 registry is supported through a research grant from Actelion Pharmaceuticals Ltd

New text

The TOPP-2 registry is supported through a research grant from Actelion Pharmaceuticals Ltd (now Janssen Pharmaceuticals)

Rationale for change

The text was updated to reflect a change in the name of the company providing financial support.

2. Responsible parties (page 6)

Old text

- Damien Bonnet, Paris, France (chairman of Association for PePH)
- Maurice Beghetti, Geneva, Switzerland
- Rolf Berger, Groningen, The Netherlands
- Tilman Humpl, Bern, Switzerland
- Dunbar Ivy, Denver, USA

New text

- Maurice Beghetti, Geneva, Switzerland (chairman of Association for PePH)

- Rolf Berger, Groningen, The Netherlands
- Damien Bonnet, Paris, France
- Tilman Humpl, Lörrach, Germany
- Dunbar Ivy, Denver, USA

Rationale for change

The Board member list was updated according to the current status.

2. Responsible parties (page 6)

Old text

The Association for PePH receives a research grant for TOPP-2 from Actelion Pharmaceuticals Ltd for 6 years. Actelion is not involved in the management of, nor in the decisions related to, the registry and will not have access to the database.

The Association will provide Actelion once yearly with a report of fully anonymized, aggregated results on patient characteristics and patient medication use in the registry.

Furthermore, Actelion has the opportunity to request specific analyses that will be provided only after approval of the TOPP-2 EB. Agreement for such analyses will not be unreasonably withheld.

Scientific collaboration between the TOPP-2 investigators and Actelion employees using registry data can be initiated after agreement of the TOPP-2 EB. The content and scope of such collaboration will then be described in concert with involved parties.

New text

The Association for PePH receives a research grant for TOPP-2 from Actelion Pharmaceuticals Ltd (now Janssen Pharmaceuticals Ltd) for 6 years. Janssen is not involved in the management of, nor in the decisions related to, the registry and will not have access to the database.

The Association will provide Janssen once yearly with a report of fully anonymized, aggregated results on patient characteristics and patient medication use in the registry.

Furthermore, Janssen has the opportunity to request specific analyses that will be provided only after approval of the TOPP-2 EB. Agreement for such analyses will not be unreasonably withheld.

Scientific collaboration between the TOPP-2 investigators and Janssen employees using registry data can be initiated after agreement of the TOPP-2 EB. The content and scope of such collaboration will then be described in concert with involved parties.

Rationale for change

he text was updated to reflect a change in the name of the company providing financial support.

4. Milestones (page 7)

Old text

- Q2 2015: First new incident patient included into TOPP-2
- Q4 2021: Last patient included into TOPP-2 and TOPP-2 database closure

New text

- Q2 2015: First new incident patient included into TOPP-2
- Q2 2021: Last patient included into TOPP-2 (enrollment closure)
- Q4 2022: TOPP-2 database closure

Rationale for change

Enrollment into the registry has slowed down over time and has been stably low for the last 2 years. Additionally, preliminary data analysis from the TOPP-1 registry has revealed that a large proportion of outcome events in pediatric patients with PH occur within 12 months after diagnosis. In the interest of capturing as many outcome events as possible, the registry design has been modified to allow the documentation of 18 months of follow-up for all patients. This is achieved by closing enrollment 6 months ahead of time and simultaneously extending the runtime by 12 months.

5. Rationale and background (page 7)

Old text

The TOPP-1 global registry for pediatric PH (groups 1, 3, 4 and 5) started in January 2008. Since then, and as of June 2014, data from over 680 children with PH have been included; of those, over 50% were newly diagnosed patients. Median follow-up since inclusion is approximately 3.5 years for the total cohort and 2.5 years for incident patients. Data from TOPP-1 on patient characteristics (1), diagnostic approach (2), baseline hemodynamics (3), treatment (4) and acute vasodilator response tests (5) have been published. Manuscripts on outcome (solely based on incident patients) and ABCD categories are in preparation.

New text

The TOPP-1 global registry for pediatric PH (groups 1, 3, 4 and 5) started in January 2008. Since then, and as of June 2014, data from over 680 children with PH have been included; of those, over 50% were newly diagnosed patients. Median follow-up since inclusion is approximately 3.5 years for the total cohort and 2.5 years for incident patients. Data from TOPP-1 on patient characteristics (1), diagnostic approach (2), baseline hemodynamics (3), treatment (4), acute vasodilator response tests (5) and event rates (6) have been published. Manuscripts on outcome (solely based on incident patients) and ABCD categories are in preparation.

Rationale for change

The publication list was updated to reflect the current status.

7.2 Timelines (page 8)

Old text

The inclusion period will run until registry closure. Registry closure is scheduled for 31 December 2021. Per 27 July 2018 247 patients were enrolled into the TOPP-2 registry. Approximately 440 patients are expected to be enrolled until registry closure.

New text

The inclusion period will run until 30 June 2021. Registry closure is scheduled for 31 December 2022, i.e. all patients will have at least 18 months of follow-up. Per 11 June 2021, 382 patients were enrolled into the TOPP-2 registry; approximately 385 patients are expected to be enrolled until enrollment closure.

Rationale for change

The timelines and the recruitment target were updated to reflect the early enrollment closure and the runtime extension (see rationale for 4. Milestones).

7.6 Study size (page 13)

Old text

TOPP-2 met its initial enrollment goal of 200 patients in September 2017. To further support the power of the registry, enrollment will remain open until registry closure, which is scheduled for 31 December 2018. Per 27 July 2018 247 patients were enrolled into the TOPP-2 registry. Approximately 440 patients are expected to be enrolled until registry closure.

New text

TOPP-2 met its initial enrollment goal of 200 patients in September 2017. To further support the power of the registry, enrollment will remain open until 30 June 2021, i.e. 18 months prior to registry closure, which is scheduled for 31 December 2022. Per 11 June 2021, 380 patients were enrolled into the TOPP-2 registry. Approximately 385 patients are expected to be enrolled until enrollment closure.

Rationale for change

The timelines and the recruitment target were updated to reflect the early enrollment closure and the runtime extension (see rationale for 4. Milestones).

9 Management and reporting of adverse events/adverse reactions (page 18)

Old text

This registry is made possible through a research grant from Actelion Pharmaceuticals Ltd, marketing authorization holder for products used to treat PH. Patients included in TOPP-2 might be treated with these products.

To make sure Actelion can comply with its worldwide pharmacovigilance regulatory obligations, the Association has a system in place for its CRO to identify and follow-up potentially reportable adverse events for Actelion's products of which the Association becomes aware through the TOPP-2 registry.

New text

This registry is made possible through a research grant from Actelion Pharmaceuticals Ltd (now Janssen Pharmaceuticals), marketing authorization holder for products used to treat PH. Patients included in TOPP-2 might be treated with these products.

To make sure Janssen can comply with its worldwide pharmacovigilance regulatory obligations, the Association has a system in place for its CRO to identify and follow-up potentially reportable adverse events for Janssen's products of which the Association becomes aware through the TOPP-2 registry.

Rationale for change

The text was updated to reflect a change in the name of the company providing financial support.

Annex 1: Publication policy (page 21)

Old text

The TOPP-2 registry is supported by a research grant from Actelion Pharmaceuticals Ltd. As acknowledgment of this support, the Association has agreed to furnish Actelion any draft publication in connection with the TOPP-2 registry for preview and comments at least 30 days prior to planned submission of the manuscript. Actelion's financial support will be acknowledged in all publications and presentations based on TOPP-2.

New text

The TOPP-2 registry is supported by a research grant from Actelion Pharmaceuticals Ltd. (now Janssen Pharmaceuticals Ltd). As acknowledgment of this support, the Association has agreed to furnish Janssen any draft publication in connection with the TOPP-2 registry for preview and comments at least 30 days prior to planned submission of the manuscript. Janssen's financial support will be acknowledged in all publications and presentations based on TOPP-2.

Rationale for change

The text was updated to reflect a change in the name of the company providing financial support.