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LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – multicentre, randomized cross-over clinical trial protocol

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Title: LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – multicentre, randomized cross-over clinical trial protocol

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ABSTRACT

Introduction

Attention deficit hyperactivity disorder (ADHD), which affects 5-10% of the general pediatric population, was reported to be more common in children with T1D in whom it ADHD exacerbates the clinical course of T1D. Proper pharmacological treatment of ADHD in such patients may thus have a beneficial neurological and metabolic impact. To address this issue, we designed a non-commercial 2nd phase clinical trial comparing the impact of different pharmacological interventions for ADHD in children with T1D.

Methods and analysis

The study is a multicentre, randomized, open-label, cross-over clinical trial in children and adolescents with ADHD and T1D. The Trial will be conducted in four reference pediatric diabetes centres in Poland. Over 36 months, all eligible patients with both diagnoses of T1D and ADHD (aged 8-16.5 years, T1D duration >1 year) will be offered participation in the Trial. Patients will be enrolled in an online once-weekly parental training in behavior management for ten weeks. Afterward, they will be randomized to pharmacotherapy groups: methylphenidate (long-release capsule, doses 18-36-54mg) versus lisdexamphetamine (doses 30-50-70mg). Treatment will continue for 6 months before switching to alternative medication. Throughout the Trial, the participants will be evaluated every three months by their diabetologist and online psychological assessments. The primary endpoint (ADHD symptom severity in the Conners 3.0 questionnaire) will be assessed by a blinded investigator. Secondary endpoints will include HbA1c, CGM indices, and Quality of Life (PedsQL).

Ethics and dissemination

The trial is approved by the local Bioethical Committee and Polish administrative body (RNN/142/22/KE, UR/DBL/D/263/2022). The Trial results will be used to improve ADHD treatment in children with T1D. Treatment efficacy and the dual psychiatric and metabolic benefits will be used to evaluate the economic feasibility of using LDX in patients with both diseases. Additionally, the Trial will promote collaboration between mental health professionals and diabetes teams.

Strengths and limitations of this study

Strengths:

- Multicentre trial on a vulnerable population and complex, unaddressed clinical issue of neurodevelopmental and metabolic comorbidity.
- Blinded assessment of primary endpoint, use of structured and validated questionnaires for diagnosis and assessment.
- Direct comparison of drugs via cross-over design with planned dose-optimization protocol.

Limitations:

- Patients and physicians not blinded to the drug, possible expectation bias.
- A moderate risk of selection bias – exclusion of patients with more complex psychiatric phenotypes. Caregivers and patients reluctant to stimulant medication drugs may be unwilling to participate.

Keywords:
Attention-deficit hyperactivity disorder, type 1 diabetes, methylphenidate, lisdexamphetamine, clinical trial, HbA1c,

Introduction

ADHD effect on type 1 diabetes treatment

Type 1 diabetes (T1D) is a common metabolic disease in childhood affecting over one million young people worldwide, with an age-standardised incidence of 31/100,000 in Europe, and 16/100,000 in Poland (0-19 years, per 100,000 per year)[1,2].

Recent advantages in medical technology improved glycemic control and significantly reduced rates of diabetes complications[3,4]. However, state-of-art therapy of T1D is highly demanding for the patient as it requires multiple actions throughout the day e.g. frequent blood glucose monitoring, counting of carbohydrates intake, and adjustments of administered insulin doses. To benefit from such intensive treatment, a child needs efficient executive functioning and a high level of self-control – and those who lack those abilities might face the gap between expected and achieved outcomes.

In particular, comorbid psychological and neurodevelopmental disorders, including attention-deficit/hyperactivity disorder (ADHD), were shown to impair diabetes management[5–8]. ADHD is a neurodevelopmental disorder affecting 5-10% children[9]. The problem of ADHD is especially relevant due to the reported 35% (OR 1.35; 95% CI: 1.08–1.73) increased risk of ADHD in patients with T1D compared to healthy peers[10]. A Swedish active screening of children with T1D showed that among children with newly diagnosed ADHD, 77.8% had inadequate metabolic control (mean HbA1c>8.6%) compared to 42.9% in the group of children with treated ADHD[11]. Association between ADHD and poor T1D control were reported by German and Israeli studies[12,13]. As a result of deteriorated metabolic control, those patients experience an elevated risk of life-threatening episodes of severe hypoglycemia or ketoacidosis, resulting in prolonged hospitalizations[10,14,15] and long-term complications, such as diabetic nephropathy[5]. In that perspective the need for evidence regarding the effectiveness and safety of ADHD treatment in pediatric T1D emerges as a pertinent clinical challenge.

Current ADHD treatments and their effects on type 1 diabetes

No randomized clinical trials (RCT) have been conducted regarding the effectiveness and safety of ADHD treatment with coexisting T1D. Therefore, despite the tremendous impact that both conditions have on patients' everyday life, current clinical guidelines on the psychological management of T1D do not address the problem of ADHD[16].

Many European therapeutic guidelines recommend environmental modifications or psychosocial intervention as first-line treatment for children with ADHD[17–19]. Parent training in behavior management (PT) is a psychosocial intervention aimed at improving caregiver's understanding of ADHD symptoms and helping them acquire skills to deal with everyday challenging behavior and support child development. Although PT improves parenting and reduces conduct problems, meta-analyses found no effect of PT on core ADHD symptoms when raters were blinded to the treatment allocations[20]. If, despite PT, symptoms of ADHD persist and cause significant impairment of daily functioning, pharmacotherapy is recommended.

Two psychostimulants with well documented effect and tolerability in ADHD are methylphenidate (MPH) and lisdexamphetamine (LDX). Stimulants have higher effect sizes on ADHD core symptom reduction than non-psychostimulating medications and their dosage is easier to adjust[21,22]. In Poland, long-acting MPH formulations are considered the first-line pharmacotherapy for ADHD[23]. LDX, contrary to MPH, is an inactive prodrug that requires enzymatic conversion, resulting in an extended and more stable acting time (~13h). In most international guidelines, LDX is advised first line treatment comparable to long-acting MPH, or as a secondary drug after treatment failure with previous MPH medication attempts[22]. In Poland LDX is neither reimbursed by the National Health Fund (NHF) nor commercially available.

Limited retrospective data demonstrates that patients with ADHD and T1D treated with stimulants show lower HbA1c (8.1±1.0%) compared to children that were diagnosed but not treated pharmacologically (8.5±1.1%)[24]. At the same time, others reported higher blood pressure and no difference in metabolic control[12,13]. However, generalization of those results remains limited due to the low sample size, lack of evidence from RCTs, and no direct comparisons between LDX and MPH. In conclusion, there is a lack of data on the safety and effectiveness of ADHD medication in children with T1D regarding the effect on ADHD symptoms, quality of life, and metabolic control.

The aim of the Study

The Trial aims to compare the safety and efficacy of ADHD treatment with LDX or MPH in children and adolescents with ADHD and T1D in improving ADHD symptoms, T1D control, and patient's quality of life.

Methods and analysis

Study design and population

LAMAinDiab is a phase 2 randomized cross-over open clinical trial with blinded endpoint assessment. The project is funded by the Medical Research Agency. This public agency provides financing for non-commercial clinical trials in Poland through open calls. Upon application for financing of the trial, the project consortium was established, and four recruiting sites – that collectively provide care for ~25% of national pediatric population with T1D[25,26] – were declared within the grant application and remained unchanged thereafter.

Patient and Public Involvement statement

The project`s idea was consulted with and supported by a national patient organization (Polish Federation for Support of Children and Adolescents with Diabetes, “Diabetycy.eu”). As a result, the organization entered consortium leading the project. Clinical trial`s design and protocol were thoroughly consulted with the organization, and its representative (MZ) was included among the authors to acknowledge her input. Subsequently, the organization`s qualified representatives agreed to play the roles of independent investigators blinded to the treatment allocation and perform ADHD symptom assessments for participating children.

Inclusion and exclusion criteria

Principal inclusion criteria:

- Age 8-16.5 years at trial entry;
- T1D diagnosed according to National and International Guidelines[27,28] at least 12 months before recruitment, treated with functional intensive insulin therapy,
- ADHD diagnosis according to 5th Edition Diagnostic and Statistical Manual of Mental Disorders (DSM-5)[29] or International Statistical Classification of Diseases (ICD-10)[30] and confirmed as consistent with DSM-5 by a psychiatrist;
- Polish citizenship and health insurance.

Principal exclusion criteria:

- Clinical partial remission of T1D (daily insulin dose<0.3 j/kg and concomitant HbA1c measurement ≤6.5% from the last 3 months) or severely unsatisfactory glycemic control (mean HbA1c over the past year ≥12%, excluding HbA1c measurement at T1D diagnosis);
- Clinically apparent or previously-diagnosed cardiovascular disease: hemodynamically significant heart defect, advanced vascular atherosclerosis, or documented hypertension (at least stage 2);
- Diagnosed intellectual disability or other disability that prevents patient adherence to its therapeutic regimen; history of other mental illness or disorder preventing participation in the trial, e.g. bipolar disorder, schizophrenia, other psychotic disorders, history of suicide attempts or present suicide intentions, psychoactive substances abuse;
- Contraindications to either studied drug.Language barrier making it impossible to conduct a full psychological consultation in Polish, lack of permanent residence and national insurance in Poland;
- Inability of the parents/legal guardians' to come to the Centre at the time specified by the protocol, in particular – to pick up the study drugs at the dose adjustment stage (the need to pick up 4-5 times over 6-8 weeks, each time within 2-3 days of receiving the recommendations);
- Other reasons that, in the opinion of the attending physician, are more likely to result in difficulties in maintaining the participant's participation in the trial or harm to the participant's health in case of participation in the trial.

Setting

The Trial will be conducted in 4 pediatric diabetology centres, and apply telemedical tools to facilitate recruitment, improve compliance and reduce the burden on participants and their families. The participating centres provide coordinated pediatric diabetology care for their respective voivodeships (regions of Poland):

- Lodzkie voivodeship: Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Pediatric Centre of the Central Clinical Hospital of the Medical University of Lodz;
- Silesian voivodeship: Department of Children's Diabetology, Medical University of Silesia, Upper Silesian John Paul II Child Health Centre;

- Pomeranian voivodeship: Department of Pediatrics, Diabetology, and Endocrinology of the Medical University of Gdansk, University Clinical Centre in Gdansk;
- Opole voivodeship: Department of Pediatrics of the Institute of Medical Sciences of the University of Opole (Department of Pediatrics and the Diabetology Clinic for Children of the University Clinical Hospital in Opole).

Information about the centres was published on the project's website - https://lamaindiab.umed.pl/. Pediatric diabetology centres included in the trial are public care providers – the trial visits and procedures will be carried out as add-ons to routine visits related to the management of diabetes. Pediatric healthcare in Poland is tax-financed by the NHF and provides universal, free-of-charge care for all children registered in Poland and their caregivers.

Summary of trial procedures

Patients with ADHD and T1D, meeting the clinical trial's inclusion criteria may enroll into the Trial in the designated reference centres. First, their guardians will receive information about the study from the centre`s representative via phone, followed by complete Information and Consent forms sent to agreed mail address. During the next routine outpatient consultation, the guardians and children will thoroughly discuss the information provided with an investigator. After answering any questions related to the study and its protocol, the investigator will verify inclusion and exclusion criteria and obtain signed informed consent form in line with current regulations (from both parents and children ≥13y.o.). After successful recruitment, study procedures will be initiated. Simplified patient's course in the clinical trial is demonstrated in Figure 1.

[FIGURE 1]

Each patient will begin the Trial starting with the enrollment appointment, followed by a baseline assessment by a diabetologist and a psychological evaluation. At this stage, all trial participants will be provided with Sponsor-funded devices, including pre-configured tablets with appropriate telecommunication software and prepaid internet access, wrist accelerometers, and blood pressure monitors. Additionally, willing patients who did not qualify for reimbursement will be provided with continuous glucose monitoring (CGM) sensors and receivers and instructed in their use.

Next, the patient's parents/legal guardians will participate in a PT program of 10 themed online workshops (90 minutes long) led by psychotherapists and supplemented with homework and educational materials. PT aims to provide immediate educational and behavioral support for the child's caretakers by educating them about ADHD and providing tools and skills to understand and modify the child's behaviors and was demonstrated to strengthen family bonds and improve adherence to future pharmacotherapy. To successfully complete this phase of the Trial, participant's guardians must participate in at least 8 meetings – with a possible revisit of the missed ones in another cycle.

After completion of PT, each participant will repeat the psychological evaluation to assess the effects of PT intervention alone on ADHD symptoms severity. Those with sustained clinically-significant ADHD symptoms will be qualified for pharmacological intervention. Possible contraindications for pharmacotherapy will be assessed during the next diabetological visit.

The add-on procedures will include urine tests (pregnancy and panel test for substance us), ECG with QT segment assessment (to exclude longQT syndrome) and ophthalmological consultation (to exclude glaucoma). Subsequent and final assessment and qualification will be performed by psychiatrist during an online consultation. Afterward, each participant starting pharmacotherapy will be randomized using a digital randomization system to receive either MPH or LDX as the first drug.

The dose will be optimized during up to four biweekly psychiatric consultations. After the maximum tolerated dose is established, patients will continue pharmacotherapy for 6 months. During that time, treatment safety and efficacy will be evaluated twice - after first 3 months by psychological and diabetes care team's evaluation (with small dose adjustments allowed) and after full course (6 months) of therapy. On-demand psychiatric consultations will be allowed. In addition, during both diabetological visits each participant will donate a dry blood sample for evaluation of the concentration of an allocated drug, and another sample will be self-collected on the day of the final psychological assessment for that arm to ensure that endpoint measurements are not biased by incidental non-adherence. After the last evaluation, participants will return the unused drug to their diabetes care centre and will begin a wash-out period.

Qualification for the second arm of pharmacotherapy will be based on the same procedures and consultations which will be performed in parallel with the last diabetological assessment in the first arm. Final switch and start of the second drug (LDX or MPH) will be based on psychiatrist decision. Dose adjustment, safety and efficacy monitoring will follow the same procedures over the next 6 months. Schedule of the Trial's procedures was presented in Table 1.

[TABLE 1]

At the end of patient's participation in the Trial, all the Sponsor-funded devices will be returned, and the last safety and efficacy interview will be performed. All the patients will receive further treatment recommendations at NHF facilities.

Randomization

The starting drug will be determined using block randomization stratified by the trial centrein a 1:1 ratio between MPH and LDX as the first drug. The risk of randomization or protocol breakage error will be minimized by using a user-friendly "Randomizer" IT tool provided by the Sponsor, integrated with the eCRF. In the event of unexpected randomization difficulties (e.g., lack of internet access or other technical problems), centre's trial-coordinator may request randomization via backup randomization list available only for sponsor's representative, re-randomization or patient's withdrawal.

Blinding

The participant allocation is open both to the participant and their guardians as well as their attending physician (diabetologist and psychiatrics alike). However, the people assessing the primary outcome (i.e. ADHD symptom severity) will be blinded to the allocation and operating independently from the care centres. No exceptions or unblinding options are planned for

those researchers as their assessment serves mostly research purpose, and data collected by them are reviewed by unblinded clinicians.

Endpoints and analysis

The **primary endpoints** of the Trial are:

1. Efficacy, defined as change in the intensity of ADHD symptoms ("inattention" and "hyperactivity/impulsivity" measured by Conners 3 questionnaire) compared between LDX vs. MPH.
2. Safety, defined as frequency of MedDRA-defined adverse events for both drugs.

For each participant, we will calculate the difference in questionnaire scores ("inattention" and "hyperactivity/impulsivity") at the end of each arm versus the initiation of drug therapy (before first drug). Separate comparisons will be made for each subscale and informant (guardian/child).

Safety analysis will report the number of recorded events by type and severity and the incidence rate (the number of events divided by the number of patient-months of observation).

The **secondary endpoints** of the Trial are (all compared between LDX and MPH arms):

1. Diabetes control, as measured by HbA1c and CGM-derived time in target range, mean sensor glucose, and coefficient of variation, before and after treatment with each of investigated drugs;
2. General and diabetes-related quality of life (measured with PedsQL QoL and diab questionnaires), before and after treatment with each of investigated drugs;
3. Number and percentage of trial participants that achieved improvement of ADHD symptoms (Conners 3 "inattention" and "hyperactivity/impulsivity") defined as 33% reduction in scale values compared to baseline.

The **exploratory endpoints** of the Trial are:

1. Difference between LDX vs. MPH in school attendance during the month preceding the 6-month drug evaluation;
2. Difference between LDX vs. MPH in physical activity (daily steps, % of time in moderate-to-vigorous physical activity) and sleep (duration, latency, efficiency) indices;
3. Differences between baseline assessment and after PTBM completion concerning: in ADHD symptoms severity (Conners 3 "inattention" and "hyperactivity/impulsivity"), HbA1c and CGM-derived glycemic control (time in range, mean sensor glucose, coefficient of variation);
4. Difference between LDX vs. MPH in frequency (number of events per patient-months) of acute diabetes complications (severe hypoglycemia, ketoacidosis) and hospitalizations, and number of days spent in inpatient care (number of days per patient-months).

Tools and parameters used during the Trial

During in-patient visits in the Trial, standard procedures will be performed, including anthropometric, heart rate, and blood pressure measurements. Applicable values will be referenced with Polish percentile charts.

ADHD symptoms will be measured using The Conners' Rating Scales (The Conners 3.0 scales, Polish version) completed by parents (Conners 3.0-P) and children (Conners 3.0-SR). The Conners' Rating Scales are validated and most commonly used tools to assess difficulties in children and adolescents with ADHD in research and clinical settings worldwide. The Polish version of Conners 3.0 has proven high psychometric reliability and validity. In the Trial, we will focus on changes in content scales of "Inattention" and "Hyperactivity/Impulsivity", core two domains of ADHD symptoms by DSM5[29].

Diabetes control will be assessed using HbA1c measured in local laboratories using methods concordant with the NGSP program. Moreover, patients will be instructed to use continuous glucose monitoring (CGM) according to their leading physicians' recommendations and generated data will be collected during diabetes check-ups. In Poland, CGM is reimbursed in the form of intermittently-scanned CGM, with possible extension into real-time CGM for those with impaired awareness of hypoglycemia. If available, CGMs will be linked with appropriate devices: insulin pumps, CGM readers, mobile phones. CGM data will be backed up and processed using GlyCulator 3.0 platform[31]. For wrist accelerometer data, manufacturer-provided software will be used to collect the data for further analysis.

Patient's quality-of-life (QoL) will be measured using the Pediatric Quality of Life Inventory 3.2 Core (PedsQL QoL) and Diabetes Module (PedsQL diab)[32]. The PedsQL is the most common tool to measure QoL in the pediatric population. The PedsQL Diabetes Module allows focusing on T1D-specific issues, especially relevant for the ADHD interaction with T1D self-control. PedsQL QoL and diab have been translated into Polish and validated for academic and commercial use.

During the drug dose-optimization period, patients will be tasked with performing self-assessment, including self-monitoring of blood pressure using automated monitors, diabetes monitoring with CGM, and activity monitoring using a wrist accelerometer. Blood pressure monitors data will be periodically uploaded into a central data repository integrated with electronic case report forms (eCRF), while wrist accelerometry will be stored and analysed at the Trial completion. CGM data will be backed up on in-patient clinic visits using appropriate software in each centre.

Statistical analysis

The primary outcome will be compared between the LDX and MPH group using paired t-tests and multivariable regression models to account for clinical covariates. Sensitivity analysis will be performed for primary and secondary endpoints for the subgroup of patients with no imputed data.

For each intervention, the % of reported adverse events will be reported with the relevant statistics for paired comparisons (Chi2, p), and for the entire table (T_{MB}, p).The incidence rates for individual adverse events will be compared with appropriate statistical tests (Poisson test

or equivalent). In addition, each type of event will be compared using the McNemar test, and the frequencies of different events using the McNemar-Bowker global symmetry test.

Treatment safety will be assessed and reported following standard procedures and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and WHO severity scale, and recorded in eCRF.

Safety and efficacy endpoints will be analysed using data from patients who completed both planned treatments, independent of potential protocol deviations (i.e., population "as treated"). Data of patients lost to follow-up will be filled in on the basis of last-observation carried forward, provided that they have at least one complete timepoint of outcome measures on the current treatment. Patients with deviations from protocol leading to no outcome data will not be included in efficacy analyses.

The secondary and exploratory endpoints will be evaluated using the appropriate statistical methods for either continuous (paired t-test, linear regression) or nominal variables (McNemar test). Interim analyses were not planned within this study.

Sample size estimation

To our knowledge, at the time of planning this Trial, no trial with equivalent design and outcome measures in this population was published. Thus, we calculated the sample size to allow for detection of a moderate difference (0.33 standard deviations) difference in score changes between LDX vs. MPH for the key Conners 3 measures[33]. Such difference was deemed clinically-impactful by the clinical team designing the trial. To estimate the sample size, we assumed significance threshold of alpha=0.05, the statistical power of 80%. The risk of applying multiple tests (each scale in each type of responder – four in total) was assessed as minimal due to high intercorrelations among those measures. As such, no alpha adjustment was planned. Such assumptions yielded the minimum number of participants of 89 (rounded to 90). The risk of drop-out during pharmacotherapy was assessed as considerable (~33%) due to the challenging population of interest (children with ADHD and T1D, with ADHD possibly present in parents) and known side effects of tested medications. Thus, the target number of pharmacologically-treated children was planned at 135, and 150 recruited given that up to 10% might be disqualified from pharmacotherapy due to drug contraindications or considerable improvement after PT. Assuming recruitment success at 80% (considerable benefit for patients, access to a drug unavailable in Poland, coordinated diabetes and psychiatric care), we estimated that 190 children that should be approached. Based on the general prevalence of ADHD in the pediatric population, the number of patients with T1D to screen for ADHD would be at least 4000 – which was a number of patients supervised by the 4 Trial centres.

Data entry and storage

Patient data collected during the clinical Trial will be stored within the electronic trial documentation database, following appropriate regulations, with data access provided to appropriate trial personnel. Reported, presented, and published data will be anonymized. The clinical trial records will be stored for 25 years after trial completion.

Trial monitoring

Trial monitoring will follow adequate international and national clinical trial regulations. Sponsor's representatives will visit each site, discuss the clinical trial course, review and validate relevant records, and verify all reference centres' that partake in the clinical trial. National regulatory authorities may request access to research documentation, source documents, research personnel, and facilities. The Sponsor will be notified of any centre's audits by regulatory agencies, and copies of audit reports will be transferred accordingly.

Ethics and dissemination

Ethical considerations

The clinical trial follows principles of the Helsinki Declaration, current Good Clinical Practice guidelines, and other applicable regulations. The clinical trial has been registered in European Union Drug Regulating Authorities Clinical Trials Database (no. 2022-001906-24) and in ClinicalTrials.gov (NCT05957055). The clinical trial was approved by the appropriate bioethical committee (agreement no. RNN/142/22/KE), and the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (UR/DBL/D/263/2022). All participants of the clinical trial are insured within the appropriate insurance agreements (policy no. COR233280) and signed informed consent forms from them and their parents will be collected before trial procedures. All changes in the Trial are subject to ethical and regulatory review before their incorporation into the clinical trial.

Safety during and post intervention

Before the intervention, the treatment of coexisting diseases will be recorded in the eCRF and continued as is or appropriately modified by the respective specialist. All adverse events will be documented in the electronic trial documentation using MedDRA v24.1 and graded using applicable WHO standards, with SAE reported within 24 hours since the occurrence and evaluated by Safety Monitoring Team (SMT). In case of a SUSAR, the SMT follows the Council for International Organizations of Medical Sciences forms and reports it to appropriate authorities within 15 days (or 7 in case of threat to the life or death of the patient) from receiving the report, following the data transfer procedure with the applicable law. The SMT will provide an annual patient safety report throughout the clinical trial, including appropriate information on treatment safety. The Sponsor holds the right to pause or discontinue part of the trial, the entire trial, or the participation of an individual patient.

After trial completion, all the patients will receive further treatment instructions, prescription for ADHD treatment and referral to appropriate health provider facilities. Reference diabetology centres will provide continued diabetes care under NHF.

Dissemination plan

Results will be submitted for publication in leading international scientific journals in diabetes care, endocrinology and psychiatry. Results will also be shared during relevant national and international congresses and conferences. The cooperation between the Sponsor and patient organization (affiliation 13) will be continued after the Trial's completion to increase awareness of the impact of psychiatric diseases in patients with T1D.

Discussion

Despite the favorable opinion of the Polish Agency for Health Technology Assessment and Tariff System, LDX is still unavailable for Polish patients outside this clinical trial. We will provide data collected during this Trial for consideration of the Agency, to promote discussion about the availability of LDX and advocate for it being widely accessible (if not reimbursed). We will also perform a specific cost-effectiveness analysis for the particular population of children with ADHD and T1D, and investigate possible costs and benefits of considering LDX as a first-line treatment in this group of patients, justified by the system savings provided by possibly-improved diabetes control.

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clinical trial protocol and written the supplementary materials; BM, ASz, ACh, PJCh, MM, IM, AK, TW, WF, AB – consulted the manuscript and the clinical trial protocol; MZ –supervied patients consultation of the clinical trial. All authors reviewed the results and approved the final version of the manuscript. We comply to the ICMJE guidelines.

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Competing interest statement: No competing interests to declare.

Table 1. Study schedule. The order of treatment (A/B) will be decided at randomization (allocation step). Names of visits corresponding to Figure 1 are included.

			STUDY PERIOD										
			Enroll	PT	Allocate	Post-allocation							
	DURATION		*1 week*	*10-22 weeks*	*1 week*	*First treatment (6 months)*				*Second treatment (6 months)*			
ENROLLMENT	Eligibility screen		X		X				X				
	Informed consent		X										
	Randomization (to A/B)				X								
INTERVENTION	Parent training in behaviour management			X									
	Cross-over	MPH				A	A	A	A	B	B	B	B
		LDX				B	B	B	B	A	A	A	A
ASSESSMENTS	Conners 3, PedsQL questionnaires		Psychological evaluatlion 1		Psychological evaluation 2		Psychological evaluation 3		Psychological evaluaton 4		Psychological evaluaton 5		Psychological evaluaton 6
	Diabetes control (HbA1c, CGM)		Diabetological visit 1		Diabetological visit 2		Diabetological visit 3		Diabetological visit 4		Diabetological visit 5		Diabetological visit 6
	Anthropometric, BP, HR measruement												
	Urine tests, ECG with QT segment assessment, ophthalmologic consultation												
	Psychiatric consultation				LDX/MPH qualification	Dose optimization		*Additional dose adjustment		Dose optimization		*Additional dose adjustment	Referral to care under National Health Fund

576

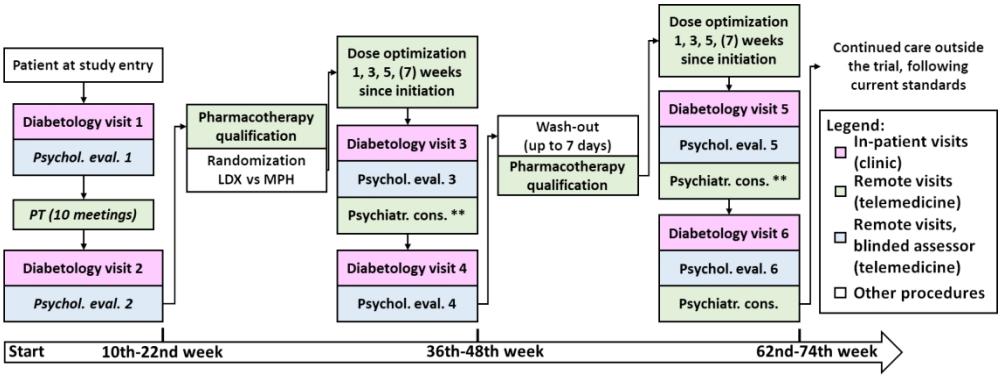

Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH – methylphenidate. ** - if needed on-demand consultation

315x117mm (150 x 150 DPI)

Supplementary File 1: model consent form and other related documentation given to participants and authorised surrogates

Information for the parent/legal guardian

Information for the parent/legal guardian

LAMAinDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD and type 1 diabetes - a randomized crossover clinical trial

Study sponsor: Medical University of Lodz

Primary researcher:

Research facility (full name, address, telephone):

Researcher:

Researcher's phone number:

Patient number: _____

Preface

Dear Parent/Legal guardian,

We are contacting you because your child is 8-16.5 years old and suffers from type 1 diabetes (T1D) and attention-deficit hyperactivity disorder (ADHD). This makes them eligible for participation in the "LAMAinDiab" clinical trial, which aims to improve ADHD therapy and, indirectly, diabetes control. We would like to invite you to participate in this study. The following information will help you understand the purpose of the study and how your participation might look. Please read it carefully. You can also discuss your child's participation in the study with family, friends, or other physicians outside of the study team. We encourage your children to be included in the discussion and decision-making process to the extent of their capacity. If you have any doubts or questions, ask your doctor for clarification.

The study you are invited to is a non-commercial clinical trial sponsored by the Medical University of Lodz, and funded by a Polish government institution, called the Medical Research Agency (ABM). The study is non-commercial, which means that its sponsor cannot make financial profits related to the conducted trial - including applying for registration or marketing authorization of a drug or using the results of the study for marketing purposes. However, these results can be used to change everyday clinical practice and improve the quality of treatment and patients' lives. We intend to include 150 children in the study.

Introduction

The LAMAinDiab study focuses on two chronic diseases: type 1 diabetes (T1D) and attention-deficit hyperactivity disorder (ADHD). Diabetes is a disease that, as you know very well, requires frequent control of the child's blood sugar level and therapeutic decisions to be made many times a day: calculation of insulin doses, corrective doses, administration of carbohydrates, etc. Some of these decisions are made by you as a Parent/Legal guardian, but over time, more and more of them will belong to your child.

ADHD, on the other hand, is a disorder that makes a child easily distracted by external stimuli, have trouble concentrating on one activity, forget about daily tasks or finish work that has been started. It is a common disorder, affecting about 5% of children according to current research – although only one-fifth of them are diagnosed. If left untreated, it can lead to school difficulties as well as make it

much harder to manage diabetes on a daily basis. Forgetting to measure sugar levels, frequent mistakes when counting carbohydrates, or missed meals/insulin boluses - some of these events may be related to your child's additional illness and are neither his nor your fault. ADHD coexisting with T1D increases the risk of life-threatening acute complications of diabetes, frequent hospitalizations, and long-term, life-shortening chronic complications. Untreated ADHD can lead to complications in the form of poorer school performance, aggressive and antisocial behavior, anxiety and depression disorders, problems with psychoactive substance abuse, and also increases the risk of accidents and deaths due to them. As part of the LAMAinDiab study, we want to provide your child with the best ADHD treatment in accordance with current guidelines, including access to drugs absent on the Polish market, as well as adapted to diabetes therapy. We believe that proper treatment of ADHD will not only improve the quality of your child's life but also make it easier for him to control diabetes.

What is the standard of ADHD treatment - and how can your child benefit from participation in a clinical trial?

There are two main strategies to treat ADHD. The first one is educating parents/legal guardians on how to effectively deal with child`s difficult behaviors and support them in coping with the disorder. The other, crucial element is taking medications that help reduce the symptoms of ADHD, i.e. improve attention and facilitate impulse control. In Poland, there are currently several drugs registered and available for the treatment of ADHD in children, with methylphenidate (MPH) being one of the most commonly used.

Unfortunately, combining drugs used to treat ADHD with diabetes therapy is difficult, and few doctors are able to reconcile the two therapies. Moreover, both in Poland and in the world, there are no specific guidelines for the treatment of ADHD in the particular group of patients with T1D. As a result, the therapy, including the choice of drug, is most often based on general guidelines as well as individual assessment and clinical experience of the doctor. For this reason the metabolic control of diabetes, which is so important for your child, is rarely taken into account when assessing the effectiveness and effect of drugs in ADHD.

LAMAinDiab is designed to provide your child with care delivered by experts who are familiar with both diseases. Your child will be under the care of a well-coordinated team, which will also include you as parents/legal guardians. In addition, as part of the study, we will provide your child with access to a new ADHD drug, lisdexamfetamine (LDX). It is a drug with proven safety and high efficiency, but not available on the Polish market. During the study, you will be able to assess which of the tested drugs (LDX or MPH) works better in treating your child's ADHD. Your child's participation in the study will ensure that they receive the best possible of care and will allow us to create standards which will hopefully improve the care of children with ADHD and T1D throughout Poland in the future.

What is a clinical trial, and why are such studies needed?

Research into the optimal treatment of ADHD has been ongoing for 75 years. New drugs, tested all over the world, give children hope for better functioning. These are difficult studies to conduct because they require children, as well as their parents, to take some risks and invest trust in the treatment plan prepared by the research team. Often the new treatment turns out to be better than the old one - but not always. It is clinical trials like this that tell us what works well - and what needs to be improved. People participating in clinical trials, including children and adolescents, are treated according to specific rules, the so-called Research Protocol. In addition, they are closely monitored to ensure that the treatment is safe and effective.

In the case of people with T1D and ADHD, such studies do not yet exist - so we do not know what treatment might be best for your child. That is why we want to ask you for your help and participation in the LAMAinDiab study to help test two drugs - methylphenidate (MPH) and lisdexamfetamine (LDX). Both are known, safe, and effective drugs in the treatment of ADHD - but we do not know which one will be better for your child and how exactly their use can help in the treatment of T1D. Therefore, if your child takes part in the study, he/she will receive both of these medicines in a random order. This is the first study that will allow us to answer many questions, but above all, provide your child and others struggling with this problem with the best possible therapy! The protocol of this study was designed by physicians and specialists in both diabetes and ADHD treatment – in part also from your Diabetes Clinic.

Purpose and course of the study

The aim of the study is to compare the effectiveness of LDX and MPH in reducing ADHD symptoms in a child, as well as to assess the effect of the treatment on T1D control and the child's quality of life.

If you choose to have your child participate in the study, you will be asked to sign a document called the Informed Consent Form. This document should be signed by both Parents/Legal guardians taking care of the child. Remember to discuss all issues related to the child's participation in the study together and with the child to the extentof their understanding. If you have any questions or concerns, please ask any of the researchers and we will try to answer them to the best of our ability. In addition, girls who could become pregnant and who are sexually-active will be asked to use contraception throughout the period of participation in the study. Those who have not started engaging in sexual activities will be asked to maintain sexual abstinence.

Remember that the consent for the child's participation in the study must be signed by both parents, so please - if you can, consult and agree on this matter before visiting the Diabetes Clinic. In the case of children from 13 years of age, their signature is also required. If you all consent to your child's participation in the study, but it is not possible to collect all signatures (e.g. due to the absence of one of the parents at the appointment), we will ask the absent person for verbal (telephone) consent in the presence of witnesses - and to sign the document during the next appointment. If one of the parents is permanently absent or deprived of parental rights, the consent of one parent supported by appropriate documents is sufficient. In the event of disagreement between the legal guardians or legal guardians and the child, the case may be settled by the guardianship court.

After agreeing to participate in the study, your child will be required to follow the planned treatment protocol and doctor's recommendations - please help them in this by explaining the next steps of the study and encouraging to participate in study visits. You and your child will also be required to report all disturbing events observed in your child such as unwelcome symptoms or deterioration of health, even minor ones such as colds, headaches, and sleep problems. Keeping accurate records of these so-called adverse events helps us to ensure that the treatment proposed in the protocol is safe.

Treatment in the study will take place in your current diabetes clinic - and at home, using online appointments. This way, you will be in constant contact with us and will not have to travel further than your Diabetes Clinic.

After starting participation in the study, your child will be invited for the first appointment to the center - i.e., your Diabetes Clinic. During it, the child will undergo a full physical examination, and his/her health and development will be assessed, as well as diabetes control - similar to a standard diabetes appointment. A drop of capillary blood will also be taken from child’s finger to measure glycated hemoglobin.

During this appointment, you will be provided with the equipment necessary to participate in the study. First, you will receive a tablet with internet access and applications necessary for full participation in the study. It will be lent to you for the entire duration of the study based on appropriate agreement, and the transmission of internet data will be financed from the research funds. This tablet will be used to make remote appointments with certain researchers. You will also receive an accelerometer to measure your child's activity. It will be a device in the form of a wrist watch, which, uses hand movements to estimate the number of steps taken, the intensity of physical activity, and the quality of sleep. **We do not require your child to wear the accelerometer for the entire duration of the study** - we will only ask you to wear the watch three times during the entire study, each time for 2 weeks. Importantly, we ask that your child wears it also at night because we want to assess how the treatment affects not only daily activity but also the length and quality of sleep. The exact information on the use of the accelerometer will be provided to you by the researcher when dispensing the equipment. The equipment you will receive for the purposes of the study will be lent by the Sponsor on the basis of a separate lending agreement signed by you - and should be returned at the end of the child's participation in the study. The rented equipment will have a manufacturer's warranty and valid insurance, but please treat it with care like any medical device, e.g., an insulin pump.

We would also like your child to use a Continuous Glucose Monitoring (CGM) system while participating in the study. As you probably know, this is a small subcutaneous device that resembles an insulin pump infusion set. It continuously measures the glucose concentration in the subcutaneous tissue and uses it to estimate blood glucose. It is possible that your child already uses some kind of CGM system and it is a daily routine for you. If this is the case, participation in the study does not change anything for you, we ask that you use CGM regularly and we will use the data collected by the system to assess your child's diabetes control during subsequent appointments. If your child has not used CGM before or is not currently using it - we would like to offer him the opportunity to use it during his participation in the study. In this case, your center will provide you with free CGM sensors sufficient to monitor your child between appointments, and your doctor will tell you how to use them. We strongly encourage you to use CGM, although it is not mandatory in this study - we believe that it will make it easier for you to control diabetes and will ease the burden of finger pricking and capillary blood glucose measurements.

Then, within a few days since your first appointment in the center, you will have your first teleconsultation with a researcher outside of your Diabetes Clinic. During it, the investigator will perform two surveys with you. The first is the detailed Conners 3 questionnaire, which assesses the intensity of ADHD symptoms. The examination will consist of asking the child and then the parent/legal guardian a series of questions assessing the daily functioning of the child. The second questionnaire (PedsQL) will assess the child's quality of life, both general and diabetes-related. Here, too, the researcher will ask you and your child a number of questions. The entire examination should not take more than 30-40 minutes. This study and all the questions asked during it will be repeated in subsequent teleconsultations of this kind - and are extremely important for the success of the study. Therefore, we ask for your patience and understanding, as well as to explain to your child why we ask the same questions from time to time. We do this to reliably assess the change in the severity of the child's ADHD symptoms and his quality of life at the beginning of the study and in the subsequent stages of treatment - which will allow us to compare the effectiveness of the interventions and medications used.

After this initial assessment, we will ask you to participate in training for parents/legal guardians of children with ADHD. Its goal is to familiarize you with ADHD as a disorder and to teach you how to work with your child on correcting problematic behaviors. Meetings will take place online in groups of

several people, once a week for 10 weeks. Each meeting will last approximately 90 minutes. The meetings will be conducted by an experienced specialist in psychoeducation who will answers your questions about ADHD and show you how to work with your child. In addition, you will have the opportunity to talk and exchange experiences with parents of other children suffering from ADHD and T1D. After each meeting, you will also receive a set of educational materials and tasks to work on at home. At least one parent/legal guardian of a given child should attend each meeting. To proceed to the next stages of the study, yoy must complete at least 8 meetings in the series. If more than 2 meetings are missed, you can retake them in the following 10-week cycle.

After the end workshops, you will participate in another teleconsultation assessing the symptoms of ADHD and the quality of your child's life. If the symptoms of ADHD are still detectable during this examination and at the appropriate level, the child will be eligible to receive pharmacotherapy. Remember that most children with ADHD require the use of medication, and education (such as a completed series of workshops) is aimed at improving their performance - so the risk that the child will be disqualified from the study at this stage is very low.

Next, we will invite you for another appointment at your diabetes care center. Apart from full physical examination, assessment of the child's development and diabetes control, and diabetologist consultation, your child will undergo: ophthalmologist consultation, ECG, laboratory tests (blood count, HbA1c concentration, thyroid hormones). Their aim is to check for possible contraindications to the studied drugs – clinically-relevant heart disease, glaucoma etc. There is small risk that at this stage your child miht be disqualified from pharmacological treatment if the tests and consultations reveal important health problems. In such circumstances, continued participation in the study and use of studied medications could not be safe for your child. In such case (and in any case when your child finishes their participation in the study, either prematurely or not) you will receive information about places you can receive ADHD treatment within public healthcare.

During this appointment, urine samples will also be taken from your child for a drug screening test and (in the case of girls) a pregnancy test. Both the use of psychoactive substances and pregnancy are hard contraidndications to the use of the tested drugs.

During the appointment, you will also receive a blood pressure monitor for automatic blood pressure measurements at home. Aftyer the start of pharmacotherapy, we will ask you to perform (or supervise) regular blood pressure measurements in your child, as the tested drugs may slightly increase it.

After the appointment at the center, there will be a teleconsultation with another investigator: a resident physician or a specialist in child and adolescent psychiatry. During this appointment, the investigator will qualify your child, based on the medical history and available test results and consultations, to receive pharmacotherapy in a clinical trial. During the study, we will evaluate the effectiveness of two drugs: MPH in a long-acting form and LDX. Your child will take both medicines sequentially: methylphenidate for 6 months first, then lisdexamfetamine for 6 months, or vice versa (lisdexamfetamine first and then methylphenidate).

The order of drugs used in the study will be determined randomly – this makes the results more reliable. After drawing the first drug, the doctor will inform you and your child about its exact characteristics, method of administration and will answer your questions and doubts.

After the end of the 6-month treatment with one of the drugs, a separate qualification will take place before starting the other. The risk that your child will be disqualified from the study at this stage is very low because both drugs have the same contraindications - we just want to check if anything significant has happened in the child's medical history after half a year of treatment.

Once treatment has started, your child will receive a predetermined starting dose, which will then be adjusted to meet his/her individual needs over the next 5 weeks. After 1, 3, and 5 weeks since starting the drug, you will participate in further online appointments with the same investigator, who will assess the effectiveness of the current dose based on information from you and your child and adjust it if necessary.

During the dose adjusting process (for the first 5 weeks of treatment) we will ask you to measure your child's blood pressure every two days, two times a day (in the morning before school and after school between 2-6 pm,), and to observe behavior and appetite child.

After each of these appointments (including the first), you will receive a prescription for the study drug, which you will have to take to your Diabetes Center. Due to the legal regulations of clinical trials, the drug can only be collected in the study center.

We hope that during these appointments we will be able to determine the most optimal dose of medicine for your child, but if not, an additional appointment after another two weeks will be possible to ensure that your child is being treated in the best possible way.

During this time, we will ask you, as the child's guardian, to regularly collect the medicine from the Center and return unused medicines or empty packaging of the studied drugs.

Once we have determined the right dose of medicine, your child will take it for 6 months (so the next 21 weeks), every day, at a fixed dose. During this time, we will ask you to measure the child's blood pressure once a week, on a fixed day of the week, at a fixed time (it may be a weekend).

After 3 months, we will invite your child for a check-up appointment at the Center, during which we will carry out standard diabetic consultation procedures: physical examination, including weight, height, and blood pressure measurements, medical interview, assessment of diabetes control, capillary blood collection from the finger to measure glycated hemoglobin concentration. In addition, we will then collect capillary blood from the finger (4 drops) on a special paper in an amount similar to that needed to measure blood glucose with a glucometer. It will then be sent (marked with the number of clinical trial participant) to the laboratory in order to measure the concentration of the administered drug in a dry blood sample. This will allow us to assess whether the child is using the prescribed study drug regularly. At this visit, you will also receive a single home dry blood spot kit and instructions on how to use it. This is not very different from measuring your blood glucose with a glucose meter. We will ask you to collect a dried blood sample from the child once on a fixed date before the next stationary appointment. It is a collection of capillary blood, such a drop as for blood glucose testing using a glucometer. At this appointment, you will be dispensed a supply of medicine for the next 3 months.

At the same time, within a maximum of a week from the appointment at the Center, another teleconsultation will be held, with the assessment of the intensity of ADHD symptoms (Conners 3 questionnaire) and the quality of life (PedsQL).

After 6 months from the start of pharmacotherapy, your child will undergo another psychological assessment in the form of a teleconsultation- this will be the last assessment of ADHD symptoms and quality of life during treatment with a given drug.

Then, we will again invite your child to the appointment at the Center. This time, in addition to a diabetes consultation and physical examination, the doctor will conduct the tests necessary to start the second drug. Similar to the previous qualification appointment, these will include: an ophthalmologist consultation, ECG, and laboratory tests (blood count, HbA1c concentration, ferritin

concentration, thyroid hormones). Urine samples will also be taken for a pregnancy test and a drug screening test. We will also collect a dried blood spot sample, similarly to the previous visit. After the tests are performed, a psychiatric teleconsultation will be held again in order to start the second drug. The course of treatment will be identical to that of the first drug (5 weeks of dose selection, stationary appointment + psychological assessment after 3 and 6 months).

At the end of the study (after completion of pharmacotherapy with both drugs or at any other time in the event of withdrawal of consent or disqualification from the study), we will invite you and your child to the last appointment at the center, during which the investigator will examine the child, discuss recommendations for further care and collect the loaned equipment: tablet, accelerometer, and blood pressure monitor.

What do I need to know about the drugs used in the study?

The methylphenidate (MPH) used in the study is an oral extended-release capsule medication used as a first-line treatment for ADHD in children. After oral administration of the product, the active substance (methylphenidate) is gradually released over the next few hours. Peak blood concentrations are reached approximately 6 to 8 hours after taking, after which the blood concentration of methylphenidate gradually decreases.

Lisdexamfetamine (LDX) is a prodrug, meaning a molecule that becomes an effective drug only after being modified by the body. In this case, oral administration of lisdexamfetamine is followed by rapid absorption from the gastrointestinal tract followed by hydrolysis to dexamfetamine, which is responsible for the drug's pharmacological effect. This gives it a more stable profile and a longer operating time (up to 13 hours). It is a new drug, available on the American and European markets for several years. Unfortunately, LDX is not currently available on the Polish market.

Side effects

Like any drug, both methylphenidate and lisdexamfetamine have been tested for side effects. The most common ones are listed below. Most of them are mild and do not interfere with your child's daily functioning. However, if they occur during the study, their severity will be analyzed on a case-by-case basis may be an argument to stop child`s participation in the study. All side effects during the study will be monitored and reported, and your child will be given appropriate help if they experience them.

Methylphenidate

Very common (may affect more than 1 in 10 people)

insomnia, nervousness, headaches.

Common (may affect up to 1 in 10 people)

nasopharyngitis, anorexia, decreased appetite, a moderate decrease in weight gain and height during prolonged use in children, emotional lability, aggression, agitation, anxiety, depression, irritability, abnormal behavior, dizziness, dyskinesia, psychomotor hyperactivity, somnolence, arrhythmia, tachycardia, palpitations, hypertension, cough, pharyngolaryngeal pain, abdominal pain, diarrhea, nausea, abdominal discomfort, vomiting, dry mouth, alopecia, itching, rash, hives, joint pain, fever, growth retardation with prolonged use in children, changes in blood pressure and heart rate (usually increased), body mass reduction.

Uncommon (may affect up to 1 in 100 people)

hypersensitivity reactions such as angioedema, anaphylactic reactions, ears edema, blistering, skin peeling, hives, itching, rash, skin eczema, mental disorders, auditory, visual, and tactile hallucinations, anger, suicidal thoughts, mood changes and swings, nervousness, tearfulness, tics, aggravation of existing tics in the Tourette's syndrome, hypervigilance, sleep disorders, suicide attempts (including completed suicide), transient depressive mood, abnormal thinking, apathy, repetitive behavior, hyper concentration, sedation, tremor, diplopia, blurring of vision, chest pain, dyspnea, constipation, liver enzymes increased, angioedema, bullous conditions, exfoliation, myalgia, muscle convulsions, hematuria, fatigue, heart murmurs.

Rare (may affect up to 1 in 1,000 people)

mania, confusion, libido disorder, convulsions, choreoathetotic movements, reversible ischemic neurological disorders, neuroleptic malignant syndrome (NMS; reports poorly documented, in most cases patients also received other drugs. The role of methylphenidate in these cases is uncertain), difficulty in accommodation, mydriasis, visual disturbance, angina pectoris, hyperhidrosis, rash macular, erythema, gynecomastia.

Very rare (may affect up to 1 in 10,000 people)

anemia, leukopenia, thrombocytopenia, thrombocytopenic purpura, cardiac arrest, myocardial infarction, inflammation and/or occlusion of cerebral arteries, distal freezing, Raynaud's phenomenon, hepatic dysfunction (including hepatic coma), erythema multiforme, dermatitis exfoliative persistent drug rash, muscle spasms, sudden cardiac death, blood alkaline phosphatase increased, bilirubin increased, platelet count decreased, white blood cell count abnormal.

Not known (frequency cannot be estimated from the available data).

pancytopenia, delusions, thinking disorders, confused states, cases of abuse and addiction have been described, more often for immediate-release formulations, cerebrovascular disorders (including vasculitis, cerebral hemorrhage, cerebral arteritis, cerebral vascular embolism), grand seizures mal, migraine, supraventricular tachycardia, bradycardia, ventricular extrasystoles, extrasystoles, chest discomfort, very high fever.

Lisdexamfetamine

Very common (may affect more than 1 in 10 people)

decreased appetite, weight loss, difficulty sleeping, dry mouth, abdominal pain, headache

Common (may affect up to 1 in 10 people)

uneven heartbeat (palpitations), chest pain (may be a sign of heart disease), agitation, nervousness, anxiety, depression, aggression, irritability or mood swings, severe sleepiness, tiredness or restlessness, difficulty getting or keeping an erection or changes in libido, dizziness, uncontrollable spasms, involuntary muscle movements or tremors, shaking or unusual activity, irregular or rapid heartbeat (tachycardia), shortness of breath, nausea, vomiting or diarrhea, constipation, fever or sweating, rash, teeth grinding

Uncommon (may affect up to 1 in 100 people)

seeing, feeling, or hearing things that are not there (hallucinations), being over-excited, being over-active, having no inhibitions (mania), allergic reactions (hypersensitivity), shortness of breath or swelling of the legs (signs of heart disease) talking, feeling depressed, anxious, depressed or restless (dysphoria), feeling happy and excited (euphoria), frequent skin picking, uncontrollable muscle spasms

or sudden body movements, itching, rash or red itchy patches (hives), blurred vision, dilated pupils, poor blood circulation which causes numbness and whiteness fingers and toes (Raynaud's phenomenon), high blood pressure, metallic taste or changes in taste (dysgeusia), fainting

Not known (frequency cannot be estimated from the available data)

severe allergic reactions with a rapid drop in blood pressure, shortness of breath and itching/hives (anaphylactic reaction), seeing, feeling, or hearing things that are not there, paranoia, delusions (psychotic symptoms), convulsions (seizures), abnormal heart rhythm, life-threatening irregular heart rhythm (seen on an electrocardiogram), allergic liver damage which may be accompanied by yellow eyes and/or skin (eosinophilic hepatitis), swelling of the skin (angioedema) or a severe rash with blisters on the skin and mucous membranes (Stevens-Johnson syndrome).

In addition, if the Research Team obtains new information related to the clinical trial that may affect your child's further participation, you and your child will be immediately informed by the doctors from your facility.

Does my child have to take part in the study?

No, regardless of the consent to participate in the study, your child will remain under constant diabetes care in accordance with the standards of care in Poland.

Are there other alternative treatments available?

Methylphenidate is the first-line treatment for ADHD in children. Other used drugs include atomoxetine, reboxetine, and clonidine, but they are less effective in reducing ADHD symptoms. They may be appropriate in particular cases, e.g. in the presence of methylphenidate intolerance or the presence of additional disorders/diseases.

Lisdexamfetamine is currently unavailable on the Polish market.

What medical procedures will be performed in connection with participation in the study and what risks may result from their performance?

Despite the experience of the staff and the diligence of medical procedures, the occurrence of complications cannot be ruled out. The main medical procedures and their possible complications are listed below:

- **Physical examination**: non-invasive procedure.
- **Blood sampling**: weakness and fainting after blood sampling, injection site infection, local allergic reactions.
- **Sampling for dry blood spot testing:** dirtying/infection at the puncture site, local allergic reactions.
- **Collecting a urine sample for a pregnancy test and a multitest for psychoactive substances**: a non-invasive procedure
- **Electrocardiography (ECG)**: non-invasive procedure.
- **Blood pressure measurement**: non-invasive procedure
- **Accelerometer sleep and activity monitoring**: local allergic reactions
- **Glucose monitoring using CGM**: infections of the skin and subcutaneous tissue at the sensor site, local allergic reactions

Prior to each procedure, the study physician will discuss with you the exact course of the procedure and the associated benefits/risks.

Sample storage (biobanking) and additional tests

Samples collected during treatment, such as blood, blood serum, and dry blood drop test strips, will be stored in research centers in Łódź, Gdańsk, Katowice, or Opole. The storage time of patients' biological samples was set at 5 years from the end of treatment. Information about the stored material will be available to you and your parents/legal guardians.

Complementary tests should help us better understand the causes of your condition and how your medications work and identify further risk factors. The aim is also to treat patients more effectively according to their individual regimens.

What are my child's responsibilities as a study participant and mine as a participant's Parent/Guardian?

If you consent to your child's participation in the study, it will be your and your child's responsibility to follow the recommendations of the doctor conducting the study (Investigator), and to report any disturbing symptoms regarding the child's health. Certain medications must not be used during the study. Therefore, before participating in this study, the study doctor (Investigator) will check if your child is not taking these medications or has stopped taking them early enough. Some medicines may require dose adjustments. Inform the study doctor (Investigator) before your child starts and/or changes any medications, including over-the-counter medications. The study doctor (Investigator) may decide to withdraw your child from the study for medical reasons (e.g. occurrence of a serious adverse event or a serious adverse reaction to a medicinal product), in the event of non-compliance with the instructions of the doctor conducting the study (Investigator), or for other important medical reasons.

Do I have to pay for the medicines my child will receive?

The drugs in the study are provided by the Sponsor (Medical University of Lodz) free of charge. It is necessary to collect drugs at research centers designated for this purpose.

Your child's participation in the study is completely free and you do not have to incur any costs. You will not be financially compensated for your child's participation in the study, and you will not be reimbursed for time and travel expenses that may be necessary for study site visits.

Who can I contact if I have questions or problems?

If you have any questions, problems, or concerns about any part of the study, or if you believe your child has been harmed as a result of this study, you may contact the Primary Investigator or your child's study doctor. You can also discuss any doubts or concerns about the study with them at any time. We will do our best to give you a satisfactory answer (please use the contact details at the end of the Information).

If you have any questions about your child's rights as a research participant, or any problems that you feel cannot be discussed with the Researchers, you can contact the independent Bioethics Committee that issued a positive opinion about the research. Contact details are indicated below:

Bioethics Committee at the Medical University of Lodz
Pl. Hallera 18, 90-647 Lodz
II floor, room 230
phone number: 785 911 596, 42-272-52-43, 42-272-52-44
e-mail: bioetyka@umed.lodz.pl

You can also contact the Patient Ombudsman if you have questions or concerns you would like to discuss with someone outside of the research team. Contact details:

Office of the Patient Ombudsman/Patients Rights Office
Młynarska 46 street
01-171 Warsaw
Mon.: 9.00-18.00, Tue-Fri.: 9.00-15.00 or via phone number: 800-190-590 (Mon.-Fri.: 8.00-18.00).

Clinical trial insurance

Under applicable law, the research Sponsor and the researcher are covered by civil liability insurance for damages caused by the act or omission of the insured, which took place during the period of insurance cover, in connection with the conduct of the research.

The relevant policy number for this study is: COR285781

A copy of the policy along with the terms and conditions of insurance is at the Principal Investigator conducting the study and will be available for inspection.

You can report any damages arising in connection with participation in the study directly to the insurer.

In the event of any damage arising in connection with participation in a clinical trial, the participant is entitled to free treatment of the said damage.

What will happen to the results of the study after its completion?

After the end of the study, that is, after the last visit of the last participant in the study, the collected information will be analyzed, presented at scientific conferences, and published in recognized medical journals. The results of the study may be used to change the current ADHD and T1D treatment guidelines, as well as to develop new therapies. The identity of the patients who participated in the study will remain anonymous.

What happens to samples taken from my child during the test?

Blood samples collected during visits and dry blood sample blotting papers that remain after laboratory testing will be retained for 5 years after the end of the study in case new therapeutic options become available to target specific genetic variants associated with ADHD or diabetes. Urine samples will not be stored and will be destroyed. During one of the diabetic blood collection appointments, we will collect two additional blood samples from your child for future research projects. They will be marked only with your child's Patient number (without identifying data) and then sent to the Medical University of Lodz, where they will be stored for a maximum of 5 years. The samples will be used in a separate medical experiment and reviewed by the relevant Bioethics Committee.

Who verified the study?

The study was reviewed and approved for by an independent Bioethics Committee at the Medical University of Lodz, which is responsible for ensuring that all study participants are properly informed about the risks associated with the study and that the decision to participate is a voluntary choice. The President of the Office for Registration of Medicinal Products, Medical Devices, and Biocidal Products also approved the study.

Will my child's participation in the study be confidential?

Yes. All information collected about your child in connection with the study will be processed in accordance with generally applicable law, in particular with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation) (hereinafter: "GDPR") and the Act of 10 May 2018 on the protection of personal data. Personal Data is processed only for the purpose of conducting the study and to the extent necessary for its implementation, and access by authorized persons (e.g. monitors or auditors) to direct medical records will be possible only on the premises of the research center. All study data will be pseudonymized and assigned a unique study number (instead of the name and surname, the data will only be marked with a code).

All detailed information on the principles of processing Personal Data can be found in the Consent Form for the Processing of Personal Data.

Informed consent form for participation in a clinical trial

LAMAinDiab – lisdexamfetamine vs methylphenidate for pediatric ADHD patients with type 1 diabetes - randomized crossover clinical trial

Patient's name:

1. I confirm that I have read and understood the **Parent/Legal Guardian Information** regarding this clinical trial. I had the opportunity to read the information provided, ask questions and receive satisfactory answers.
2. I understand that my child's participation in the study is voluntary, and I can withdraw from it at any time without giving any reason, without affecting the medical care provided and my rights.
3. I have been informed that the doctor conducting the study (Investigator) may decide to stop my child's participation in the study for medical reasons, as well as in the event of non-compliance with the recommendations
4. I consent to the researcher's access to my child's medical records prior to the commencement.
5. I agree that after the end of the study, the information collected will be analyzed, presented at conferences, published in scientific journals, and used to develop new therapies.
6. I understand that biological samples from my child will be analyzed for the purpose of this study.
7. I have read and accept the general terms and conditions of third-party liability insurance of the Sponsor and the Investigator.
8. I undertake to follow the recommendations regarding the clinical trial that will be provided to me by the Research Team.
9. I have been informed that I will receive a copy of the Parent/Legal Guardian Information and a copy of the Informed Consent Form.
10. I give my voluntary consent for my child to participate in this clinical trial
11. Consent to storage of biological material

You have the option of consenting to the Researchers using samples of biological material collected from your child for storage in research centers in Łódź, Gdańsk, Katowice, or Opole. Whatever you decide, it will not affect your child's medical care. Your child may continue to participate in the study even if you decline.

After deciding, please mark the answer with a cross

"**YES**" if you consent to the obtained biological material being stored and/or used to perform optional tests, Or "**NO**" if you do not wish to keep any samples. □ **YES** □ **NO**

Name and surname of the Parent/Legal Guardian (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)
Name and surname of the Parent/Legal Guardian (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)
Name and surname of the Researcher receiving the Consent (Capital letters or stamp)	**Date** (handwritten)	**Signature** (handwritten)

Consent form for the processing of personal data of a participant in the **LAMAinDiab clinical trial - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1 diabetes - randomized crossover clinical trial**

Patient's name:

I consent to the processing of my minor child's Personal Data in the scope of name and surname, date of birth, gender, PESEL number, and data from the shared medical documentation, for the purpose of conducting this clinical trial, as well as my Personal Data in the scope of name and surname for the purpose of proper processing and documenting the study. I declare that I have been informed about the purposes, scope, and conditions of processing Personal Data in accordance with art. 13 GDPR. I also declare that I have received a copy of the information clause, which is Appendix 1 to this form.

Name and surname of the Parent/Legal Guardian (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)
Name and surname of the Parent/Legal Guardian (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)

Appendix 1

Information clause regarding the processing of Personal Data for the purpose of conducting and controlling a clinical trial on "**LAMAinDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1 diabetes - randomized crossover clinical trial"**.

According to Art. 13 sec. 1 of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of Personal Data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (hereinafter: "GDPR"), we inform you that:

1. The administrator of the Personal Data provided by you for the purpose of conducting and controlling this clinical trial is the Medical University of Łódź, ul. Al.Kościuszki 4, 90-419 Łódź (hereinafter referred to as: "Sponsor"). These data include both the Patient's Personal Data, i.e. a minor on behalf of whom you gave consent to participate in the study, and your personal data as a legal guardian to the extent necessary for the processing and implementation of the study (hereinafter jointly referred to as: "Personal Data").
2. Contact with the Administrator is possible via the e-mail address iod@umed.lodz.pl. Regardless of the possibility of contacting the Sponsor's Personal Data Protection Officer, any questions can be directed to the Investigator who is conducting the study.
3. The Personal Data provided by you will be processed on the basis of art. 9 sec. 2 letter a) and j) of the GDPR in order to monitor the safety of pregnancy.
4. All Personal Data provided by you will be pseudonymized (instead of the name and surname, the data will be marked with a code).
5. The personal data provided by you will be made available to the Medical Research Agency with its registered office at ul. Stanisława Moniuszko 1A, 00-014 Warsaw, which is the entity financing the study. For the purpose of conducting the test, your personal data may be made available to the Research Center where the test is carried out, to an external monitor, as well as to external laboratories testing samples as part of the test.
6. Access to the data provided by you may also be obtained by authorized persons and bodies, in particular the Bioethical Committee approving the Study, as well as the Sponsor's subcontractors (including external service providers, e.g. providers of technical, ICT services, diagnostic equipment, legal services, inspection services, etc.) or partners, persons involved in conducting the study, in particular, study observers (monitors), auditors, inspectors, doctors, nursing team, as well as national institutions supervising the study, provided that the received data is kept confidential.
7. Based on the personal data provided by you, no decisions will be made in an automated manner and the data will not be subject to profiling.
8. The personal data provided by you will not be transferred to a third country outside the territory of the European Union and the European Economic Area.
9. The Personal Data provided by you for the purposes of monitoring the course of pregnancy safety will be processed for a period of 5 years, and medical documentation - if it was created - for a period of 20 years.
10. You have the right to lodge a complaint to the President of the Office for Personal Data Protection for unlawful processing of Personal Data.
11. You have the right to access the content of Personal Data and the right to rectify, delete, limit processing, the right to transfer data, the right to raise objections, the right to withdraw consent at any time without affecting the lawfulness of processing, which was made on the basis of consent before its withdrawal - within the limits specified in the law.
12. Providing your Personal Data is fully voluntary and has no impact on the implementation of the Research

Information for the Patient (8-12 years old)

Information for the Patient (8-12 y.o.)

LAMAinDiab – lisdexamfetamine against methylphenidate for pediatric patients with attention-deficit hyperactivity disorder and type 1 diabetes – randomized crossover clinical trial

Study Sponsor: **Medical University of Lodz**

Main Investigator:

Study Institution (full name, adres, telefon):

Investigator:

The telephone number for the primary physician:

Patient's number:

Hello!

We are a group of doctors and researchers who are trying to help people with diabetes to manage their disease and enjoy life – some of us you might have met at your Diabetology Clinic. We are reaching out to you because we know that other than type 1 diabetes, you also have attention-deficit hyperactivity disorder, and no one should face such challenges alone! We believe that ADHD treatment may help you feel better and improve your diabetes control. This is why we are inviting you to join our study LAMAinDiab.

At the start, we will show you what ADHD is and how it affects diabetes. Next, we will tell you about how we want to help you. The information pamphlet that you are reading right now is seven pages long. You might find some of it boring or hard to follow. Please, ask us if you are interested in something or if some things are difficult to understand. We will do our best to answer and explain all you find unclear. After completing this pamphlet, you can ask your primary physician any relevant questions.

What is ADHD?

ADHD, or attention-deficit hyperactivity disorder, affects one in 20 people – so it's even more common than diabetes! People with ADHD may find it challenging to sit down and focus on school or while doing their homework. Have you ever forgotten to measure your glucose or made a mistake while counting the required insulin? Or forgot about the meal? This may be because of ADHD.

In this study, we want to help you deal with your issues connected to ADHD and type 1 diabetes. In the LAMAinDiab, with the team of the best clinicians and researchers in Poland, we will try and make it easier for you to control diabetes and ADHD. You may be one of 150 children who will participate in this study!

How do we treat ADHD?

To treat ADHD, you need two things. First, you and your parents/guardians need to learn about ADHD and how to cope with undesired behaviors. The second, very important thing is taking medication that help „calm the storm" of ADHD. This will make it easier for you to achieve your goals. It is challenging to treat ADHD and type 1 diabetes together, so in LAMAinDiab, you will receive care from experts with significant experience in both diseases. They, together with you and your parents, will be your own care team.

As a result, it will be much easier for you to perform everyday activities. Your involvement will also help us shape new standards of care for hundreds of other children with the same issues as you.

Clinical trials and LAMAinDiab study

For over 75 years, doctors and scientists have tried to find an optimal approach to treat ADHD. New drugs, investigated worldwide, give young people chances for better lives. Those studies are difficult because they need young people like you to take some risk and trust in the proposed treatment plan. New treatments often prove better than the previous ones, but not always. This is why clinical trials are so important – they tell us what works best and how we can improve the treatment. Participants in clinical trials, including children and adolescents, are treated following a detailed set of rules called Study Protocol. Everyone, including the participants, must follow them for the trial to be adequate. This also requires frequent check-ups to ensure the treatment is safe and efficient. In people with type 1 diabetes and ADHD, there have been no such studies yet, so we need to determine which treatment can be best for you. That's why we want you to take part in the LAMAinDiab study. This study will test the performance of two drugs – methylphenidate (MPH) and lisdexamfetamine (LDX). Both of these drugs are known for their safety and effectiveness in ADHD treatment – however, we don't know yet which one will be better for you and how well they will improve your diabetes control. In this study, you will undergo treatment with both drugs, one at a time. This will allow you to decide which of those works best for you!

Experts have designed the treatment plan for treating diabetes and ADHD. It is up to your parents/guardians to agree to your participation in this clinical trial – but your decision is also very important to us.

What will this study include?

If you and your parents/guardians decide to enter this study, the first step is to sign the informed consent form. This document will be signed by your parents/guardians. Remember, that you should go through all the details and come to an agreement together. After the form is signed, you will be required to follow the physicians' recommendations and inform your parents/guardians and physicians about all unsettling symptoms and changes in your health, even those such as cold, headache or trouble sleeping. The treatment will continue at your usual diabetology clinic and at your house using remote online visits. This way, you will remain in contact with our team without needing to travel far.

If you enter the LAMAinDiab trial, you and your parents/guardians will be invited for the first visit to your diabetes care center to undergo examination by your primary diabetologist. It will be similar to your regular visits at the clinic – we will measure your body weight, height and blood pressure. Afterwards we will focus on your glycemic control and how it can be improved. We will collect blood drop for standard glycated hemoglobin measurement, which will require us to prick your finger, but you are already familiar with this procedure.

Other things will also happen. First, your parents/guardian will receive a blood pressure monitor and tablet with an internet connection for the time of your participation in the trial. Those devices will be used while trying determine the best drug dose for you. They will also limit the number of visits to the hospital because we will use the tablet to connect with you and your parents/guardians as an online visit. We are also interested in how active you are and how much sleep you get. This is important because ADHD and drugs may impact your energy levels and activity throughout the day. This is why we want to know your daily activity before and during treatment with each medication. You will get a watch with a built-in activity monitor on the first visit. While you wear it, the watch will collect data on how active you are, if you are walking, running, or sleeping. We would like you to wear this watch three times during this trial, each for two weeks. This will allow us to analyze the collected data and determine the effect of treatment while you will not need to carry the watch all the time. At the end of your participation in the trial, you will return all the borrowed devices: blood pressure monitor,

tablet, and watch with built-in activity monitor. This will allow us to download all the clinical data from those devices and prepare them for the next study participant. So please, take care of those devices.

We would like you to use continuous glucose monitoring (CGM) sensors during the trial. Those small devices, similar to insulin pump infusion sets, are put on the skin. With the tiny needle, they allow for continuous glucose level measurement which can be accessed by a mobile device or insulin pump. Maybe you already use CGM, and it is part of your everyday life. If that is so, participation in the study will not require any changes. If you are not using CGM now (never used it or used it in the past), we would like you to use one during the LAMAinDiab study. We believe using CGM will help you control your diabetes better, reducing the need for fingerpricks. If you decide to use CGM, your physician will provide you with the appropriate sensors and instruct you on how to use them properly. However, if you don't want to use CGM, they are not mandatory in this trial, even though we highly recommend you give it a try!

In addition to the visit in diabetes care centre, we will invite you for the online visit with one of the study investigators. During the visit, you will answer some questions on how much ADHD affects your daily life now – and will allow us to measure how much this will improve throughout the trial. Some of the questions you may find tedious or tiring, but they are essential! How you answer them is critical for us to understand your experiences and determine which treatment is better for you and others. With your parents, you will answer those questions multiple times throughout the study, so please answer as sincerely as possible. This will make it easier for us to notice any meaningful changes.

At the end of the trial entry visits, we will try and help you control ADHD and type 1 diabetes, just as we promised. To do it, we will use two essential methods: (1) parental education and „training" and (2) pharmacotherapy. Moreover, if you are a girl, your primary physician will discuss pregnancy prevention, which will be required during your participation in the study.

Part I: Parental education and „training"

During the first three months (10-12 weeks) of your participation in the study, your parents/guardians will participate in 10 weekly online training sessions in small groups with an education expert. During the sessions, the expert will teach your parents what ADHD is, how to manage its symptoms and help you control it. Each session will last 90 minutes and will cover training and discussion of one topic. You may think about this parental education as if they got back to school because, similarly to you, they will get some „homework" to do between classes. After the training, your parents will learn how to control best and manage difficult situations of ADHD aggravations. Some of those methods are useful in other cases and will hopefully foster a more active approach to support and care for your parents. Parental training will include scenarios and educational materials to expand your parents' knowledge of ADHD and your struggles. For the training to be completed, at least one of your parents must participate in 8 out of 10 meetings. If this is not possible during one series of sessions, there is an opportunity to participate in the remaining meeting in the next series. However, if your parents do not participate in the training, we will not be able to continue your participation in the second part of the trial.

Part II: Pharmacotherapy

After your parents finish their education sessions, we will check again if ADHD treatment is still necessary for you – maybe you and your parents working together is enough for you to control your ADHD. To make sure, we will again ask you and your parents/guardians for an online visit with our investigator, who will ask you the same questions as at the start of the study. Based on your and your

parents'/guardians' answers, the investigator will decide if ADHD still significantly affects your activity and attention – and if you are eligible for pharmacotherapy.

Before giving you any medication, we must ensure the drugs are adequate for you. Some medicines cannot be taken if there are other preexisting conditions. We will carefully evaluate your health status during a visit in diabetology clinic. This visit may take significantly longer than usual – you may need to spend up to a few hours with us. Outside standard weight and height measurement, glycated hemoglobin and diabetologist consultation, we will assess if you have any contraindications for the treatment. We will measure your blood pressure, consult you with the ophthalmologist and record your heart rhythm with ECG. We will also collect a sample of your blood for laboratory tests.

And at last, we will also need a sample of your urine – which will be checked for any other drugs that could interact with the study drugs. The urine sample will also be used for a pregnancy test if you are female. Don't worry too much about it. All those tests are routinely required in clinical trials, and we want to be sure that we know about all possible things that could affect how pharmacotherapy interacts with other substances in your blood. If the drug test gives a positive result or your parents/guardians report your use of illicit substances – we will stop your participation in the study.

After we are sure to proceed, we will ask you and your parents/guardians to participate again in an online visit with the physician, who will talko to you and then enroll you for the first treatment. The drug you will start with will be picked randomly – think about it as if it was a coin toss – heads is drug A, tails – is drug B. Such choosing method is standard in clinical trials and lets us be sure that observed effects really come from the used drug. Also, do not worry. the second drug will still be provided for you after we evaluate the effects of the first one.

After the drug selection, your physician will instruct you and your parents/guardians about the treatment procedure, how much and how often you should take the drug, and how to administer it. Please, remember, together with your parents/guardians, to take medicine systematically. If taken as advised by the physician, it will improve your control of ADHD and allow us to evaluate its effectiveness. The physician will also let you know what adverse events you may expect and what you should watch out for. Remember –adverse events may occur, but it does not mean they will necessarily happen to you. This also does not mean that the drug will not work. Finally, the physician will decide on a starting dose and write you a prescription, with which your parents can pick up the medications at the hospital.

Also, at the start of the treatment, we will ask for the severity of ADHD symptoms and your appetite. Those questions will be repeated during next online visits (after 1, 3, and 5 weeks respectively), as your physician will adjust the medication dose appropriately. This will provide you with the optimal drug dose that helps you control ADHD with the lowest risk of adverse events. During the dose adjustment period, we will ask you to carefully observe your well-being and measure your blood pressure using the provided blood pressure monitor every other day before 9 am and between 2 and 6 pm. You don't need to note those measurements down; this device will remember them and send them to your physician. During the online visits, the physician will again ask questions regarding ADHD severity and appetite and evaluate the blood pressure measurements. You will also be asked if any adverse events occurred and how frequently – so please note them as they happen. After the physician goes through all the details and collected information, they will decide if and how to adjust the dose and provide your parents/guardians with the appropriate prescription. We hope we can shoes the best dose within five weeks. However, if it proves difficult, we will plan another visit after seven weeks for the final dose adjustment and check-up. As the treatment dose is determined for you, things will slow down a bit –

your parents/guardians will get the prescription for your medication for the next few weeks, and you will no longer have to measure your blood pressure so often – now, only once per week will suffice.

After three months of treatment, we will invite you for a visit to your diabetology clinic. During this visit, the standard diabetology consultation will ensue, with height, weight and glycated hemoglobin measurement, and CGM evaluation if you decide to use the sensor. Additionally, we will collect four blood drops on a special paper strip, which will be sent to the laboratory, where our laboratory experts will measure how much of the drug is in your bloodstream. This is important because it will tell us if you did not forget about your daily dose and if the drug is absorbed and processed in your body correctly. We will also instruct you how to collect your blood on such a special paper strip, as we would like you to do so again before your next visit to the clinic. Your parents/guardians will be informed by text message on the day of sample collection. Don't worry. This will be similar to blood collection for self-monitoring blood glucose using your standard glucometer!

During this visit we can also slightly modify the dose of your medication if you or your parents/guardians want that. However, if the needed adjustment is considerable or if your diabetes care physicial sees it necessary, this will require an additional online visit.

After that visit, you will continue the treatment and measure your blood pressure once every week. After the end of the first treatment (6 months after the start), we will ask you the standard questions regarding ADHD severity during another online visit. Comparing your responses before and after six months of treatment will allow us to determine how effective the treatment was. Next, you will revisit your diabetology clinic. All the standard visit procedures will be repeated (height, weight, blood pressure, HbA1c measurement, CGM evaluation), including the above-mentioned dried blood spot collection. However, this visit again will be a longer one. Once again, we will perfofm an ophthalmology consultation and heart rhythm recording (ECG), and a blood sample will be collected for additional tests. This is required, so we are sure you are eligible for the second drug treatment. Before we start the subsequent treatment, we must be sure that the first drug is no longer in your organism – this requires a 3 to 7 days „wash-out" period. The online visit will initiate the second drug treatment, as was the case for the first drug. We will again ask questions regarding ADHD severity and begin the dose adjustment, following the same online visit plan as for the first treatment. Diabetology visits will ensue at 3 and 6 months, as for the first treatment. The last diabetology visit (after six months of the second treatment) will be your last study visit, during which we will ask you to bring all the borrowed devices and discuss your experiences in the trial.

Procedures of the study and associated inconveniences

To properly perform this study, we will need your cooperation. During the trial, you will often participate in additional visits, examinations or tests – simply, procedures. Some may seem tedious or time-consuming, and others you might not like – but thanks to you and your cooperation, we hope to make them as effortless as possible. Below, you can find a detailed description of each procedure, along with information on potential risks and associated inconveniences. If you or your parents/guardians have additional questions regarding the procedures, we are ready to provide detailed answers! Don't be afraid to ask your physician questions regarding the procedures if anything makes you curious or worried!

1) **Medical history and physical examination.** During each visits, you will be carefully examined by each Investigator. Do not worry – this will be a normal visit to the doctor and will resemble routine physician visits. Each investigator will ask you how you feel

(history taking), and while the diabetologist will examine you physically. These procedures carry no additional risk or discomfort.

2) **Glycated hemoglobin measurement from capillary blood.** Every three months, during diabetology visits, we will ask you to provide a capillary blood sample. This will be performed by a simple fingerprick that you have previously experienced many times during self-monitoring of blood glucose using a standard glucometer. This is a common procedure during diabetology visits, and although it may hurt a bit, it won't be more than you are used to.
3) **Capillary blood collection on the special paper strip – drug concentration measurement from the dry blood sample.** We will ask you three times during the study to provide a capillary blood sample (4 drops) on the special paper strip. This is required, as we will measure the drug concentration from this sample to ensure you are taking your medication and if its levels are not affected by biological processes in your body. The sample collection resembles the collection of glycated hemoglobin or self-monitoring of blood glucose. It won't hurt more than those abovementioned procedures you are already used to.
4) **Urine sample tests (pregnancy and drugs test).** For you to be eligible for the pharmacotherapy, we need to perform a few studies from the urine sample. We will ask you to provide a sample in the special container on the day of the diabetology visit.
5) **Blood pressure and heart rate measurement.** During the diabetology visits, we will measure your blood pressure using an automated blood pressure monitor – 3 times on each arm. Additionally, you will be provided a blood pressure monitor for your participation in the study, so you can measure your blood pressure when you are under treatment. This procedure may be bothersome because it requires proper preparation (you must sit down, rest and relax for a few minutes before the measurements), but we hope you will manage to do it!
6) **Anthropometric measurements.** During the control visits at the diabetology clinic, we will perform standard height and weight measurements using proper measurement devices. The measures will be carried out by trained hospital personnel.
7) **Physical activity and sleep monitoring with wristwatch with built-in activity monitor.** We will collect your data on physical activity and sleep quality during the study using a wrist activity monitor. Those measurements are not invasive and will only last for the last two weeks of parental training and during the pharmacotherapy. We ask you to wear the wristwatch with a built-in activity monitor on the wrist of your non-dominant for two weeks for 24 hours (including while you are asleep). Although it may be bothersome at the start, those watches were designed to be worn all day, and you will quickly get used to wearing them. If you want, you may continue to use the watch throughout the whole study period.
8) **Heart rhythm recording with ECG**. During the examination prior to the pharmacotherapy, we need to record your heart rhythm – this will be performed twice using a standard ECG device. This procedure is not invasive and takes only a minute.
9) **Ophthalmologist consultation**. During the examination before the pharmacotherapy, we need to measure your intraocular pressure and perform gonioscopy. Those are two routine ophthalmological procedures, and both are non-invasive. However, you may

find those measurements not comfortable. They will be performed only twice, and despite mild discomfort, they are quickly performed and should not cause any pain.

During the study, we will also use three questionnaire tools – Conners 3 (parent and child versions), PedsQL QoL and Diab (parent and child versions), appetite questionnaire and ADHD symptoms severity (Likert-scale based tests). As we already described, we will often ask you questions from those questionnaires. But it is required, as this will allow us to understand better how you manage your ADHD and type 1 diabetes and if the treatments are effective. Thanks to your answers, we can provide you with the optimal drug dose and minimize the risk of adverse events and associated discomfort. Although the visits may differ, those questions will always be asked. The questions will be asked by trained personnel with extensive experience in collecting answers and evaluating questionnaires. Please don't hesitate to ask them any questions!

General information

Your opinion is critical in the final decision on your participation in LAMAinDiab. However, you must know that the final decision is made by your parents/guardians. Suppose you and your parents/guardians will not agree for your parcitipation in the study, or decide to refuse your further particiation at any moment. In that case, you will be treated following the best current standards. Outside of this study, type 1 diabetes may be treated by a diabetologist, while a psychiatrist may help with optimal ADHD treatment.

For LAMAinDiab to be possible, it is required for many hospitals and institutions to cooperate closely. As such, some information regarding you (such as name, surname, and date of birth) and your medical and treatment history may be transferred between those institutions. Moreover, this data may be provided to regulatory agencies under some circumstances. Remember that all the people involved in this study, and those in regulatory agencies, who at any point have access to your data, must keep this data safe, protected, and held a secret.

Sample storage (biobanking) and auxiliary studies

Samples collected during this study, such as your blood, serum, and special paper strips, will be marked with your identifying number and kept at the Medical University of Lodz for five years after the study completion. The information on the storage is accessible to you and your parents/guardians. Auxillary studies that may help better understand the disease and treatment mechanism may be conducted in the future.

Contact us

If you have any more questions regarding ADHD and type 1 diabetes treatment or the LAMAinDiab study, feel free to discuss it with your parents/guardians or your physician at your convenience.

Information for the Patient (13-18 years old)

Information for the Patient (13-18 years old)

LAMAinDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD and type 1 diabetes - a randomized crossover clinical trial

Study sponsor: Medical University of Lodz

Primary researcher:

Research facility (full name, address, telephone):

Researcher:

Researcher's phone number:

Patient number: _____

Hi!

We are a group of doctors and scientists who work together to help people with diabetes cope with the disease and enjoy life - you have already met some of us in your Diabetes Clinic. We come to you because we know that in addition to type 1 diabetes, you also have an additional problem, which is ADHD. We believe that the right treatment for ADHD can help you feel better – and keep your diabetes under control. That is why we invite you to participate in the LAMAinDiab study.

First, we'll show you what ADHD is and how it relates to diabetes. Then we will tell you how we would like to help you. The information you are reading now consists of several pages of text. Therefore, please - ask about things that interest you or that you do not understand, we will try to answer as best we can and explain what is unclear. You can write down your questions and ask your doctor after reading the Information form.

What is ADHD?

ADHD, or Attention Deficit Hyperactivity Disorder, is a disorder that affects every twentieth person - so it is more common than diabetes! People with ADHD find it hard to sit still and focus e.g. at school during a lesson or while doing homework. Have you ever forgotten to measure your blood sugar or made a mistake when counting your insulin? Forgot a meal? This can be caused by this disease and not your fault. In our study, we want to help you deal with problems related to ADHD and type 1 diabetes. As part of the LAMAinDiab study, we will create conditions for you that will make it easier for you to control diabetes and ADHD.

How do we treat ADHD?

There are two main strategies to treat ADHD. The first of them is teaching you and your parents on how to effectively deal with problematic behaviors. The second, essential element is taking medications that help to "calm the storm" in your head and focus on the things you want to achieve. Unfortunately, combining these drugs with diabetes therapy is difficult, and few physicians are able to reconcile the two therapies.

The LAMAinDiab study is designed to provide you with the care of these experts who know both diseases very well. You will be under the care of a well-coordinated team, of which you will also be a part as a patient. This will ensure the highest quality of care for you, and it will allow us to create

standards thanks to which hundreds of other children and young people with similar problems will also be able to benefit from such care in the future!

Clinical trials and the LAMAinDiab study

Research into the optimal treatment of ADHD has been ongoing for 75 years. New drugs, tested all over the world, give young people hope for better functioning. These studies are difficult to conduct because they require young people like you to take some risks and trust in the treatment plan prepared by the research team. Often the new treatment turns out to be better than the old one - but not always. It is clinical trials like this that tell us what works well - and what needs to be improved. People participating in clinical trials, including children and adolescents, are treated according to specific rules, the so-called Research Protocol that they must follow. In addition, they are closely monitored to ensure that the treatment is safe and effective.

For people with type 1 diabetes and ADHD, there are no such studies yet - so we don't know what treatment might be best for you. That is why we want to ask you for your help and participation in the LAMAinDiab study. In total, we intend to ask 150 patients to take part. During the study, we would like to test the effects of two drugs - methylphenidate (MPH) and lisdexamfetamine (LDX). Both are known, good, safe, and effective drugs in the treatment of ADHD - but we don't know which one will be better for you and how their use can help you treat diabetes. If you take part in the study, you'll alternate between the two - and then you'll tell us which one makes you feel better. This is the first study that will allow us to answer many questions, but above all, provide you and others struggling with this problem with the best possible therapy!

If your parents/legal guardians consent, you will have a chance to participate in this clinical trial. However, your opinion is also very important and can influence the final decision!

How will the study be conducted?

If you and your parents/legal guardians decide to participate in the study, the first step will be to sign a document called an informed consent form. This document is signed by you and your parents/legal guardians. However, remember that you should discuss all issues together, and it should be your joint decision. After agreeing to participate in the study, you will be obliged to follow the recommendations of doctors and inform your parents/legal guardians and doctors about all disturbing symptoms and deterioration of health observed, even such as colds, headaches, and sleep problems.

Treatment in the study will take place in your current diabetes clinic - and in your home, using online consultations. This way, you will be in constant contact with us and you will not have to travel far.

If you start participating in the LAMAinDiab study, you will receive an invitation for you and your parents/legal guardians to a diabetes appointment, during which you will be thoroughly examined by your doctor. During the visit, we will measure your weight, height, and blood pressure. In addition, the doctor will analyze your diabetes control and advise you on how to manage it better. We will also take a drop of blood from your finger for a glycated hemoglobin test - as you well know, this involves a slight prick in the finger to which you are accustomed. However, since this will be a clinical trial visit, we have prepared a few extra things that will happen.

First of all, your parents/legal guardians will receive from us a blood pressure measuring device and a tablet with internet access as part of the clinical trial. These devices will be necessary to properly adjust the dose of the drug so that it meets your needs. This will also allow us to reduce the number of burdensome hospital appointments and provide you with the highest quality of treatment.

We are also interested in how active you are and whether you sleep well - this is very important because both ADHD and the study drugs can affect your energy and activity levels during the day. We will analyze what your daily activity looks like before the study drugs are administered, and how it is affected by the investigated drugs. For this purpose, during your first appointment, you will receive a wrist watch that will measure this activity. It will do this by registering your hand movements when you are sitting, walking, running, or sleeping. During the study, we will ask you to wear the watch three times for two weeks - so that we can collect the necessary data and not burden you with another device. We will also ask you to keep your watch on at night as we want to assess how your treatment affects the length and quality of your sleep.

At the end of the study, the watch, tablet, and blood pressure monitor will be returned to the hospital so that we can accurately assess your progress in the study, and the equipment will be passed on to subsequent young patients who also participate in the study. That's why we ask you - take care of the equipment you will get together with your parents!

During your participation in the study, we would like you to use continuous glucose monitoring (CGM). It is a small device resembling an insulin pump infusion set, inserted subcutaneously. It continuously tracks your blood, which you can read on your phone or insulin pump. If you use CGM on a daily basis, participation in the study does not change anything for you, and during subsequent appointments, we will use the data collected by the system to assess the control of your diabetes. If you have not used CGM before or are not currently using it - we would like to offer you the opportunity to use it while participating in the study. We believe that this will make it easier for you to control your diabetes and will allow you to measure your blood glucose level less often with a glucometer. If you decide to use CGM, your doctor will give you the sensors and tell you how to use them properly. The use of CGM is not mandatory to participate in the study, but we sincerely recommend that you at least try!

In addition to the diabetes appointment, we will also invite you to a teleconsultation with the investigator at the beginning of the study. They will ask you a series of questions to assess how much of a problem ADHD is for you - and then to measure improvement. The entire examination will take about 30-40 minutes. This study and all the questions asked during it will be repeated in subsequent teleconsultations of this kind - and are extremely important for the success of the study. Therefore, we ask for your patience and understanding. We do this to reliably assess the change in the severity of your ADHD symptoms and your quality of life at the beginning of the study and in the subsequent stages of treatment - which will allow us to compare the effectiveness of the interventions and medications used.

After these initial appointments, we will try to help you manage your ADHD and type 1 diabetes as promised. We want to do this in two ways – each of which is part of our study.

1. Education and parental "training".
2. Administration of drugs

If you are a patient who can become pregnant and have started engaging in sexual activities, you will also be asked to use effective contraception, and if you are not sexually active, the doctor will ask you to remain abstinent throughout the study.

Part I: Parental education and training.

During the first 3 months (10-12 weeks) of your participation in the study, your parents/legal guardians will participate in a series of 10 weekly online meetings in small groups with other parents of children with ADHD and an expert educator. During these meetings, an expert will explain to your parents what ADHD is, how to deal with its symptoms, and how to help you with it. Each of the 10 meetings lasts 90

minutes, during which one topic will be discussed in detail and worked through. You can think of these meetings as your parents' return to school as they will be given 'homework' from us to do between classes. After completing the training, your parents will learn methods that will make it easier for you all to control and cope with the events when ADHD symptoms get intense. This method is also effective in many other disorders. The training will also encourage and strengthen your parents' active attitude, focused on acquiring new knowledge and supporting you in new social situations. Parent training will take the form of structured group work with a prepared scenario and educational materials. These workshops are a method of expanding your parents' knowledge about your functioning and your relationship.

At least one of your parents/legal guardians must be present for 8 out of 10 meetings. If they cannot participate, they can retake up to 2 meetings during the next training cycle. The lack of participation of your parents/legal guardians in Part I of the study will unfortunately prevent you from further participating in the study.

Part II: pharmacotherapy

After your parents/guardians finish the educational meetings, we will see if you need ADHD medication at all - maybe working through appropriate behaviors with your parents is enough to make you feel good. To assess this, we will again invite you and your parents/guardians to a teleconsultation with the investigator who will ask you the same questions as at the beginning of the study. If, based on your or your parents' answers, we see that ADHD still significantly affects your activity and attention - you will receive medication as part of a clinical trial.

First, we will make sure that the medicines we want you to take are suitable for you. We will determine all this during the appointment in diabetes clinic. This appointment will be longer than usual - you will spend a few hours in your center. During them, there will be standard tests and measurements that you know: height, weight, glycated hemoglobin from capillary blood, and diabetes consultation with CGM analysis. In addition, we will check whether you have any contraindications to start a new drug. For this purpose, we will measure your blood pressure, conduct an ophthalmological examination and record your heart (ECG). We will also take your blood for laboratory tests, the results of which will be assessed by your doctor before starting treatment. Finally, we will ask you for a urine sample - we will test it for the presence of drugs. Don't stress about it, this is standard in clinical trials, we want to make sure that the drugs given will not mix with other substances that affect the nervous system. If your urine test is positive for substances other than the study drugs, your doctor will terminate your participation in the study. This will also happen if your parents/legal guardians confirm your use of illicit substances. In the case of girls, we will also perform a urine pregnancy test, as pregnancy is a contraindication to the study drug in the clinical trial.

After visiting the center, we will invite you for teleconsultations with a doctor who will decide on your treatment. They will do it based on the results of your tests and the medical interview. The drug you receive at the beginning will be chosen randomly - think of it as a roll of the dice (even result - drug A, odd result - drug B). This choice of treatment is at the heart of clinical trials and ensures that the effects of treatment really depend on the drug you receive. Also, don't worry, in this study you will have the option to try both drugs, we only draw their order.

After selecting the drug, the doctor will tell you and your parents/legal guardians about its effects, determine how much and when you should take it, and answer your questions. Please try to remember with your parents/legal guardians about taking the medicine regularly, as it will help you feel better on a daily basis and help us to evaluate its effectiveness. The doctor will also tell you what the side effects of the medicine may be and what to look for when taking it. Remember – the fact that side

effects may occur does not mean that they will happen to you, nor will they make the medicine ineffective. The doctor will issue a prescription that will allow your parents/legal guardians to collect the medicines at the Hospital. He will also ask you and your parents/guardians to specify how troublesome your ADHD symptoms are for you and what your appetite is - these questions will be repeated at subsequent visits and will help choose the right dose of medicine for you.

The dose of medicine needed is a little different for each patient, so we will be checking in on how you are feeling often! We will assign you the next teleconsultation after 1, 3, and 5 weeks of taking the drug and we will ask you to closely monitor your well-being during this time. We will also ask you to regularly measure your blood pressure with a rented device - every other day, twice: before 9:00 and between 14 and 18:00. You do not have to save the measurements anywhere - the device will remember them and send them to your doctor. During these teleconsultations, we will talk about how you assess the intensity of ADHD symptoms and appetite over the last 7 days. The doctor will analyze the results of your blood pressure measurements and ask questions about the most common side effects of the drug. The doctor will then decide whether to keep or change the dose of your medicine - and will give your parents/legal guardians a prescription for the medicine. We hope that during these 5 weeks, you will be able to find the best dose of the drug for you. If not, we will arrange an additional appointment for you and your parents/guardians after 7 weeks.

After setting the dose of the drug, things will slow down. You will receive a prescription for the drug for the next few weeks, and we will reduce the frequency of blood pressure checks (we will only ask you to check your blood pressure once a week).

After three months from the start of pharmacological treatment, you will be invited to an out-patient appointment in the clinic to undergo standard diabetes consultation. We will measure your weight and height, blood pressure, and heart rate, as well as assess diabetes control (by measuring HbA1c from a finger and downloading data from the CGM sensor). If you or your parents/guardians express such need, we may also reduce the dose of your medication during this appointment. If major changes are necessary or your diabetes doctor asks for it, then we can arrange an additional online visit with the Investigator who started your treatment with the study drug. In addition to drawing blood from your finger for HbA1c measurement, we will collect four drops of your blood on a special paper that we will send to the laboratory to check whether you took medications that day and how quickly your body processes them. We will also show you how to draw blood on this paper yourself because we would like you to do it again at home before your next visit. Don't worry, it's really easy - especially for you since you already know the glucose meter! The day when we ask you to draw blood will be determined by your doctor - we will send this information to your parents via text message.

After this appointment, you will continue your treatment for the next 3 months and measure your blood pressure once a week. At the end of this period (6 months from the start of treatment with the first drug) we will invite you to another assessment in the form of a teleconsultation, during which we will again ask you questions about your ADHD symptoms. Comparing your answers with those from earlier will allow us to assess how this drug affects your ADHD symptoms and your quality of life. After that, you will attend a diabetes appointment. During it, we will repeat the usual measurements (height, weight, blood pressure), take another blood sample on paper and assess the control of your diabetes (HbA1c measurement, CGM analysis). In addition, we will repeat the ophthalmological examination, ECG and take blood and urine samples - the results of these tests will later allow us to give you the second of the tested drugs. After this appointment, a short period will begin where you will be left without treatment. This will allow us to make sure that nothing of the study drug remains in your system when you start treatment with the other drug. Don't worry, this time it will be very short - 3 to 7 days. It will end with another teleconsultation with the doctor who started your treatment with the

first drug. During it, we will repeat the same steps as during the appointment starting treatment. The only difference is that this time we will not draw a drug for you - you will just get a second drug that you have not used yet. Thus, you will start the second, 6-month treatment period in the clinical trial. It will consist of the same stages and appointments as for the first drug - teleconsultations after 1, 3, 5 (possibly 7) weeks to select the dose, tele-assessment of ADHD symptoms, and stationary diabetes consultation after 3 and 6 months of treatment. The last diabetes consultation during this period will also the last on-site visit in the study. During this final appointment, we will pick up the loaned equipment from you and your parents, and we will ask how you enjoyed participating in the study.

Examinations performed during a clinical trial and the inconveniences that may accompany them

In order to make the study successful, we need your cooperation. You will participate in additional meetings, tests, and activities (generally: procedures). Some of them may be boring or time-consuming, and others you may not like - but with your help and cooperation, we hope to get through them quickly. Below is a detailed description of each of the procedures, along with information on the inconvenience that may accompany them. If you or your parents/legal guardians have additional questions about the procedures, we are ready to provide comprehensive answers! Don't be afraid to ask your doctor-investigator about anything that interests or worries you!

1. Examination. During each of your clinical trial appointments, we will conduct a full medical examination - this will be a normal appointment with your doctor, just like any other. The doctor examining you will always ask how you feel and if anything is wrong with you (subjective examination), and the diabetologist will additionally examine you physically (auscultate, examine your stomach, throat, etc.). All those procedures are non-invasive.
2. Capillary blood sampling and measurement of glycated hemoglobin HbA1c. Every 3 months during diabetes appointments, we will ask you to prick your finger and take a drop of blood from you. The prick may hurt - but no more than checking your blood glucose daily with a blood glucose meter.
3. Collecting a drop of capillary blood on a paper - measurement of drug concentration in a dry blood drop. Three times during the treatment, we will ask you to prick your finger and collect 4 drops of blood from you on a special paper. This paper will later go to the laboratory, where we will measure how much of the study drug was in your blood. The prick itself is similar to taking blood for glycated hemoglobin and will be done with a disposable needle.
4. Urine tests (pregnancy test and drug test) – as part of a clinical trial, in order to qualify the patient for pharmacotherapy, it is necessary to perform urine tests. We will ask you to collect urine in a special container on the day of your diabetes appointment.
5. Blood pressure and pulse measurement. During diabetes appointments, we will measure your blood pressure with an automatic blood pressure monitor - 3 times on the right and left arm. In addition, we will lend you a similar blood pressure monitor at home, which you will use to measure your blood pressure during your participation in the study. Prepare for each measurement (sit down, rest, and relax for a few minutes).
6. Body measurements - as part of follow-up appointments at the Clinic, height, and weight measurements will be performed using appropriate measuring devices, performed by trained personnel.
7. Measurement of activity and sleep quality using an accelerometer - as part of the clinical trial, data on physical activity and sleep quality will be collected using a wrist accelerometer (watch). These measurements are non-invasive and will continue for the last two weeks of psychotherapy and two 6-month pharmacotherapy cycles. The accelerometer will be worn by the study participant on the wrist of the non-dominant hand for 2 weeks around the clock (including the period of sleep). Patients will be allowed to use the accelerometer for the whole duration of the study at the reasonable request of a parent/legal guardian.

8. Electrocardiogram (ECG) - as part of recruitment for pharmacotherapy, two non-invasive recordings of the electromechanical work of the heart using ECG will be made in order to exclude functional disorders of the heart.
9. Ophthalmological consultation – before starting pharmacotherapy, an ophthalmological consultation will be carried out with non-invasive measurement of intraocular pressure and assessment of the filtration angle in order to exclude glaucoma before initiating treatment.
10. Questionnaires (Conners 3: Parent and Child, full version; PedsQL QoL and Diab, Parent, and Child, assessment of appetite and severity of ADHD symptoms - Likert scale). The questionnaires will allow us to check how you feel about ADHD symptoms and living with diabetes. Thanks to your answers, we will be able to choose the best dose of the drug for you - and also assess how effective it is. Questions will be asked by people trained for this purpose and analysis of your answers.

General information

Your opinion will be crucial in deciding whether you will take part in the LAMAinDiab study. If you and your parents do not consent to your participation in the study or withdraw it during the course of the study, you will be treated according to the best treatment available outside the clinical trial. If a patient is not participating in the LAMAinDiab trial, they will be treated according to current standards by a diabetes physician and will be referred for treatment of ADHD by a physician specialist in this field.

A study as large as the LAMAinDiab study is only possible if many hospitals and other institutions, such as laboratories, work together. Therefore, some information about you (such as your name and date of birth) and about your illness and treatment will be exchanged between these places. It may also be necessary to share information with the specialists who are supervising this study. Remember, however, that all persons who obtain information about you and your illness are obliged to maintain full confidentiality.

In addition, if the Research Team obtains new information about the clinical trial that may affect your further participation in the study, you and your parents/legal guardians will be immediately informed by the doctors from your facility. Your participation in the study is completely free. Neither you nor your parents/legal guardians will receive any financial compensation for your participation in the study.

Sample storage (biobanking) and additional tests

Samples collected during treatment, such as blood, blood serum, and test strips from a dry blood spot, will be marked only with the Patient's number (without identifying data), and then sent to the Medical University of Lodz, where they will be stored for a maximum of 5 years from the end of treatment. Information about the stored material will be available to you and your parents/legal guardians. Complementary research should help us better understand the causes of your condition and how your medications work and identify further risk factors. The aim is also to treat patients more effectively according to their individual regimens.

Please contact us if you have any further questions

If you have further questions about the disease or the LAMAinDiab study, you can discuss them with your parents or doctor at any time, including now.

Informed consent form for participation in a clinical trial

LAMAinDiab – lisdexamfetamine vs methylphenidate for pediatric ADHD patients with type 1 diabetes - randomized crossover clinical trial

Patient's name:

1. I confirm that I have read and understood the **Patient Information** regarding this clinical trial. I had the opportunity to read the information provided, ask questions, and receive satisfactory answers.
2. I understand that my participation in the study is voluntary, and I can withdraw from it at any time without giving any reason, without affecting the medical care provided and my rights.
3. I have been informed that the doctor conducting the study (Investigator) may decide to withdraw my participation in the study for medical reasons, as well as in the event of non-compliance with the recommendations
4. I consent to the researcher's access to my medical records prior to the commencement of the clinical trial.
5. I agree that after the end of the study, the information collected will be analyzed, presented at conferences, published in scientific journals, and used to develop new therapies.
6. I understand that my biological samples will be analyzed for the purpose of this study.
7. I have read and accept the general terms and conditions of third-party liability insurance of the Sponsor and the Investigator.
8. I undertake to follow the recommendations regarding the clinical trial that will be provided to me by the Research Team.
9. I have been informed that I will receive a copy of the Patients Information and a copy of the Informed Consent Form.
10. I give my voluntary consent to participate in this clinical trial
11. Consent to storage of biological material

You have the option of consenting to the Investigators using samples of biological material collected from your child for storage in research centers in Łódź, Gdańsk, Katowice, or Opole. Whatever you decide, it will not affect your medical care. You may continue to participate in the study even if you decline.

After deciding, please mark the answer with a cross

"**YES**" if you consent to the obtained biological material being stored and/or used to perform optional tests, or "**NO**" if you do not wish to keep any samples. □ **YES**□ **NO**

Name and surname of the Child (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)
Name and surname of the Investigator receiving the Consent (Capital letters or stamp)	**Date** (handwritten)	**Signature** (handwritten)

Consent form for the processing of personal data of a participant in the **LAMAinDiab clinical trial - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1 diabetes - randomized crossover clinical trial**

Patient's name:

I consent to the processing of my minor child's Personal Data in the scope of name and surname, date of birth, gender, PESEL number, and data from the shared medical documentation, for the purpose of conducting this clinical trial, as well as my Personal Data in the scope of name and surname for the purpose of proper processing and documenting the study. I declare that I have been informed about the purposes, scope, and conditions of processing Personal Data in accordance with art. 13 GDPR. I also declare that I have received a copy of the information clause, which is Appendix 1 to this form.

Name and surname of the Parent/Legal Guardian (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)
Name and surname of the Parent/Legal Guardian (Capital letters)	**Date** (handwritten)	**Signature** (handwritten)

Appendix 1

Information clause regarding the processing of Personal Data for the purpose of conducting and controlling a clinical trial on "**LAMAinDiab - lisdexamfetamine vs methylphenidate for pediatric patients with ADHD syndrome and type 1 diabetes - randomized crossover clinical trial"**.

According to Art. 13 sec. 1 of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals with regard to the processing of Personal Data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation) (hereinafter: "GDPR"), we inform you that:

1. The administrator of the Personal Data provided by you for the purpose of conducting and controlling this clinical trial is the Medical University of Łódź, ul. Al.Kościuszki 4, 90-419 Łódź (hereinafter referred to as: "Sponsor"). These data include both the Patient's Personal Data, i.e. a minor on behalf of whom you gave consent to participate in the study, and your personal data as a legal guardian to the extent necessary for the processing and implementation of the study (hereinafter jointly referred to as: "Personal Data").
2. Contact with the Administrator is possible via the e-mail address iod@umed.lodz.pl. Regardless of the possibility of contacting the Sponsor's Personal Data Protection Officer, any questions can be directed to the Investigator who is conducting the study.
3. The Personal Data provided by you will be processed on the basis of art. 9 sec. 2 letter a) and j) of the GDPR in order to monitor the safety of pregnancy.
4. All Personal Data provided by you will be pseudonymized (instead of the name and surname, the data will be marked with a code).
5. The personal data provided by you will be made available to the Medical Research Agency with its registered office at ul. Stanisława Moniuszko 1A, 00-014 Warsaw, which is the entity financing the study. For the purpose of conducting the test, your personal data may be made available to the Research Center where the test is carried out, to an external monitor, as well as to external laboratories testing samples as part of the test.
6. Access to the data provided by you may also be obtained by authorized persons and bodies, in particular the Bioethical Committee approving the Study, as well as the Sponsor's subcontractors (including external service providers, e.g. providers of technical, ICT services, diagnostic equipment, legal services, inspection services, etc.) or partners, persons involved in conducting the study, in particular, study observers (monitors), auditors, inspectors, doctors, nursing team, as well as national institutions supervising the study, provided that the received data is kept confidential.
7. Based on the personal data provided by you, no decisions will be made in an automated manner and the data will not be subject to profiling.
8. The personal data provided by you will not be transferred to a third country outside the territory of the European Union and the European Economic Area.
9. The Personal Data provided by you for the purposes of monitoring the course of pregnancy safety will be processed for a period of 5 years, and medical documentation - if it was created - for a period of 20 years.
10. You have the right to lodge a complaint to the President of the Office for Personal Data Protection for unlawful processing of Personal Data.
11. You have the right to access the content of Personal Data and the right to rectify, delete, limit processing, the right to transfer data, the right to raise objections, the right to withdraw consent at any time without affecting the lawfulness of processing, which was made on the basis of consent before its withdrawal - within the limits specified in the law.
12. Providing your Personal Data is fully voluntary and has no impact on the implementation of the Research

Administrative information:

TRIAL REGISTRATION:

Date and trial version identifier: **LAMA/2021/1, Ver. 2.0.14.11.2022, 2022-11-14**

WHO Trial Registration Data Set (1.3.1):

- Primary Registry and Trial Identyfiying Number: **UR/DBL/D/263/2022 (The Office for Registration of Medicinal Products, Medical Devices and Bioicidal Products/Urząd Rejestracji Produków Leczniczych, Wyrobów Medycznych i Produktów Biobójczych – URPL)**
- Date of Registration in Primary Registry: **2022-11-14**
- Secondary Identifying Numbers: **2022-001906-24 (EUDRA-CT), NCT05957055 (ClinicalTrials.gov)**
- Source(s) of Monetary or Material Support: ***Competition for non-commercial clinical trials in the field of psychiatry and neurology*** **(ABM/2021/2) from Medical Research Agency**
- Primary Sponsor: **Medical University of Lodz**
- Secondary Sponsor(s): **Not applicable**
- Contact for Public Queries: **Medical University of Lodz, Kościuszki 4, 90-419 Łódź, 422725239, lamaindiab@office365.umed.pl**
- Contract for Scientific Queries: **Agnieszka Butwicka, PhD, MD, Mazowiecka 15, 92-215 Łódź, +48660445966, agnieszka.butwicka@umed.lodz.pl**
- Public Title: ***LAMAinDiab - lisdexamphetamine vs methylphenidate for pediatric patients with ADHD and type 1 diabetes - a randomized cross-over clinical trial***
- Scientific Title: ***LAMAinDiab - lisdexamphetamine vs methylphenidate for pediatric patients with ADHD and type 1 diabetes - a randomized cross-over clinical trial***
- Countries of Recruitment: **Poland**
- Health Condition(s) and Problem(s) Studied: **Patients with ADHD (MedDRA 23.0 LLT 10068453, SOC 100000004873) and type I diabetes (MedDRA 21.1 PT 10067584, SOC 10027433)**
- Intervention(s): **once-daily pharmacotherapy with Elvanse (608137-32-2, SUB32146) or Concerta (prolonged-release tablet, 298-59-9, SUB03254MIG) for a duration of 6 months with initial dose optimization for 5-7 weeks, compared in a randomized cross-over setup with blinded assessment; no placebo or control group is applicable**
- Key Inclusion and Exclusion Criteria:
  - **Principal inclusion criteria:**
    - **Age 8-16.5 years at study entry;**
    - **T1D diagnosed on the basis of clinical features, presence of autoantibodies typical for type 1 diabetes (at least one of the following: anti-GAD, ICA, IAA/IA2, ZnT8) and/or low C-peptide levels (according to the laboratory standard appropriate for the assay method) and criteria for the diagnosis of diabetes according to the**

criteria of the Polish Diabetes Association and international societies:
    - an incidental glycemia ≥200mg/dl and symptoms of hyperglycemia (such as increased thirst, polyuria, weakness) or
    - two times a fasting blood glucose ≥126mg/dl or
    - a blood glucose ≥200mg/dL in the 120th minute of an oral glucose load test or
    - HbA1c ≥6.5%.
  - T1D diagnosed at least 12 months before recruitment;
  - T1D treated with functional intensive insulin therapy;
  - a diagnosis of ADHD according to DSM-5 criteria confirmed by a psychiatrist or a diagnosis of ADHD according to other criteria recognized in Poland, confirmed by an authorized person as consistent with DSM-5;
  - Polish citizenship and Polish health insurance.
- Principal exclusion criteria:
  - Daily insulin dose<0.3 j/kg and concomitant HbA1c measurement ≤6.5% from the last 3 months (clinical partial remission of T1D);
  - Severely unsatisfactory glycemic control – mean HbA1c over the past year ≥12% (not including HbA1c measurement at diagnosis of T1D);
  - Diagnosed intellectual or other disability that prevents participation in the trial or adherence to its therapeutic regimen;
  - Clinically apparent cardiovascular disease: recognized hemodynamically significant heart defect, advanced vascular atherosclerosis;
  - Diagnosis of other mental illness or disorder preventing participation in the trial, e.g. bipolar affective disorder, schizophrenia, other psychotic disorders, psychoactive substance abuse;
  - Diagnosed allergy or hypersensitivity to drugs used in pharmacological intervention -methylphenidate and/or lisdexamphetamine;
  - Language barrier making it impossible to conduct a full psychological consultation in Polish;
  - Lack of permanent residence in Poland;
  - Contraindications as reported for investigated drugs: documented hypertension (at least stage 2), positive family history for sudden cardiac deaths and atrial arrythmias in relatives below 40 y.o., clinically evident glaucoma or abnormally elevated intraocular pressure, history of suicide attempts or present suicide intentions, oppositional defiant disorder, chronic motor tics or Tourette syndrome, pregnancy or breastfeeding, short stature, underweight

(≤ 3rd percentile for reference percentile charts), epilepsy, pheochromocytoma, substance abuse or positive drug test results, prolonged treatment with sedative drugs (e.g., 1st generation antihistamines);

- **Declared by the parents/legal guardians' inability or unwillingness to come to the Center at the time specified by the protocol, in particular - to pick up the Trial drugs at the dose adjustment stage (the need to pick up 4-5 times over 6-8 weeks, each time within 2-3 days of receiving the recommendations);**
- **Other reasons that, in the opinion of the attending physician, are more likely to result in difficulties in maintaining the continuity of the participant's participation in the trial or harm to the participant's health in case of participation in the trial.**

- Study Type: **interventional, open, randomized (block randomization stratified by center), assessor masked, cross-over, phase II;**
- Date of First Enrollment: **anticipated 2023-09-01**
- Sample Size: **planned 150**
- Recruitment Status: **pending**
- Primary Outcome(s):
  - **Change of ADHD symptom severity, measured as the difference in ADHD symptom scores on the "inattention" and "hyperactivity/impulsivity" scales of the Conners 3 questionnaire (completed by patient and parent/legal guardian), before pharmacotherapy (after completion of PTBM) and the end of the 6-month course of pharmacotherapy with LDX or MPH; similar difference (before pharmacotherapy and after 6 months of therapy) for the other drug, assessed by the investigator blinded to patient allocation.**
  - **The number and frequency of adverse events (per patient-month) coded following the MedDRA dictionary, in both cycles of pharmacotherapy.**
- Key Secondary Outcomes:
  - **Improvement of metabolic control of T1D, quantified as:**
    - **The difference in HbA1c measured at the end of the MPH and LDX treatment regimen compared to the measurement before pharmacotherapy**
    - **The difference in the percentage of time patient spent in the following ranges in 14 days at the end of a MPH and LDX pharmacotherapy cycle, compared to 14 days prior pharmacotherapy initiation:**
      - **in target (70-180mg/dl)**
      - **hypoglycemia (<70mg/dl)**
      - **clinically significant hypoglycemia (<54mg/dl)**
      - **hyperglycemia (>180mg/dl)**
      - **significant hyperglycemia (>250mg/dl)**

        - **The difference in mean glycemia and coefficient of variation of glycemia (calculated as the ratio of the standard deviation of glycemia to mean glycemia, expressed as a percentage) calculated for 14 days at the end of the MPH and LDX pharmacotherapy courses, compared to 14 days prior pharmacotherapy initiation**
    - **Improvement of the subject's quality of life (QoL) from baseline, after completion of PTBM and each pharmacotherapy course. The outcome will be measured as the difference between the subject's QoL and diabetes-specific QoL (PedsQL 3.2 questionnaires, completed by patient and parent/legal guardian, assessed by an investigator blinded to patient allocation)**
    - **Number and percentage of trial participants achieving an improvement in ADHD symptom severity of at least 1/3 of the baseline value at the end of a given pharmacological intervention compared (assessed separately on the basis of "inattention" AND "hyperactivity/impulsivity" scales) (endpoint assessment by an investigator blinded to patient allocation).**
- Ethics Review: **Approved (RNN/280/21/KE), 2022-06-14, Bioethics Committee at the Medical University of Lodz, Józef Haller sq., 1B, 90-647 Łódź, Poland**
- Completion Date: **LSLV planned 2026-08-01**
- Summary Results: **Not available**
- IPD sharing statement: **No; Individual Participant Data (with Protected Health Information included) will be provided only in case of serious adverse events and suspected unexpected serious adverse reactions and only to applicable regulators and monitor institutions under appropriate regulations and applicable law.**

SPIRIT 2013 additional requirements:

- Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities:
    - **Study sponsor (Medical University of Lodz) is directly involved in: trial documentation preparation, management of electronic trial documentation, providing randomization software, statistical analysis plan preparation, pharmacovigilance and safety monitoring; Medical University of Lodz hold ultimate authority over trial documentation preparation, management of electronic trial documentation, providing randomization software, statistical analysis plan preparation, pharmacovigilance and safety montioring, and guarantees all activities follow applicable regulations.**
    - **Study funder (Medical Research Agency) is directly involved in the financial supervision of the trial, and holds ultimate authority in budget approval.**
- Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other

individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee):

- **Coordinating centre: Medical University of Lodz Representatives (1), Clinical Trials Unit Representatives (3); roles: preparation of Sponsor-Centers agreements, preparation of registration documents; responsibilities: supervision over clinical trial;**
- **Steering committee: Principal Investigator (1), Center Representatives (6), Clinical Trials Unit Representatives (3); roles: coordination of screening and trial procedures; responsibilities: organization and supervision over patient workflow in centres involved with patient recruitment and interventions;**
- **Endpoint adjudication committee: Polish Federation for Support for Children and Adolescents with Diabetes (1); roles: masked assessment of primary outcomes; responsibilities: providing assessor-blinded primary outcomes assessment for all patients after the intervention;**
- **Data management team: Department of Biostatistics and Translational Medicine (2 IT + 3 biostats); roles: preparation of data management plan and data sharing policy, assistance with preparation of registration documents and electronic trial documentation; responsibilities: supervision over crucial informatics system for the clinical trial, statistical analysis of clinical trial results following appropriate standards;**
- **Pharmacovigilance committee: Clinical Trials Unit staff (4), Principal Investigator (1), Clinical Investiagtors (2); roles: assessment, classification, reporting and submission of adverse events, drug safety monitoring and reporting; responsibilities: monitoring of patient safety during the clinical Trial;**
- **Quality assessment committee: Clinical Trials Unit Clinical Trials Unit (1); roles: assessment of all trial documentation in the context of Good Clinical Practice (GCP) and other appropriate ICH documentation, preparation, and training of Standard Operating Procedures (SOP); responsibilities: monitoring of clinical trial compliance with GCP and relevant SOP;**
- **Legal department: Clinical Trials Unit (4); roles: preparation, review, and negotiation of legal agreement; responsibilities: compliance of all trial documentation with relevant regulations.**

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1-4**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**S2: 5-8** **S2: 10**
	2b	All items from the World Health Organization Trial Registration Data Set	**S2: 4-150**
Protocol version	3	Date and version identifier	**S2: 3**
Funding	4	Sources and types of financial, material, and other support	**569-570**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**5-8** **563-568**
	5b	Name and contact information for the trial sponsor	**S2: 14** **S2: 16-19**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**151-156** **229-232** **271-272** **277-281** **570-571** **S2: 152-166**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee)	**S2: 167-201**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the Trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**87-144** **S1: 58-121** **S1: 299-410** **S1: 637-673** **S1: 885-897** **S1: 944-983**
	6b	Explanation for choice of comparators	**323-355**
Objectives	7	Specific objectives or hypotheses	**145-148** **289-322**
Trial design	8	Description of trial design including type of Trial (eg, parallel group, cross-over, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**151-152** **250-252** **S2: 98-99**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**195-215**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**167-196**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**216-273** **S2: 28-32**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**166-194** **253-269** **433-434** **S2: 311-382** **S2: 515-517** **S2: 752-757**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**258-263** **441-443** **S2: 142-147**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the Trial	**424-425**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	**289-355** **S2: 103-142**

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**Figure 1** **Table 1** **224-273**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**378-398** **S2: 101**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**151-156** **158-164** **196-226** **387-398**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**274-281**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**274-281**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**274-281**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**282-288** **S2: 28-32** **S2: 103-142** **S2: 179-182**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the Trial	**282-288**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**289-323** **323-355** **S2: 122-298** **S2: 420-431** **S2: 438-458** **S2: 674-884** **S2: 983-1195**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**237-242** **369-374**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**399-403** **S2: 174-150** **S2: 183-188**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**356-377**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**356-377**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**369-374**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**S2: 167-201**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the Trial	**423-434**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**425-434**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**404-410**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**416-418** **S2: 143-144**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**420-422**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**218-225** **S1: 509-537** **S1: 1226-1259**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**218-225** **S1: 412-419** **S1: 476-484** **S1: 898-903** **S1: 1214-1221**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the Trial	**286-288** **334-355** **366-368** **399-403** **424-433** **S1: 491-503** **S1: 538-600** **S1: 892-897** **S1: 1261-1322** **S2: 147-150**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall Trial and each study site	**571**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**405-410** **424-433** **S2: 183-188**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**438-443** **S1: 223-225**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**437-442** **S1: 51-57** **S1: 380-382** **S1: 470-475** **S1: 1209-1213**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**564-569**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**439-443** **S1: 491-503** **S1: 538-600** **S1: 892-897** **S1: 1261-1322**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**S1: 30-601** **S1: 616-906** **S1: 922-1322**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current Trial and for future use in ancillary studies, if applicable	**S1: 412-419** **S1: 476-484** **S1: 898-903** **S1: 1214-1221**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-078112.R1
Article Type:	Protocol
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Primary Subject Heading:	Paediatrics
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Title: LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting

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ABSTRACT

Introduction

Attention deficit hyperactivity disorder (ADHD) affects 5-10% of pediatric population and is reportedly more common in children with type 1 diabetes (T1D), exacerbating its clinical course. Proper treatment of ADHD in such patients may thus provide neurological and metabolic benefita . To test this, we designed a non-commercial 2nd phase clinical trial comparing the impact of different pharmacological interventions for ADHD in children with T1D.

Methods and analysis

This is a multicentre, randomized, open-label, cross-over clinical trial in children and adolescents with ADHD and T1D. The Trial will be conducted in four reference pediatric diabetes centres in Poland. Over 36 months, eligible patients with both T1D and ADHD (aged 8-16.5 years, T1D duration >1 year) will be offered participation. Patients`s guardians will undergo online once-weekly training sessions behavior management for ten weeks. Afterward, children will be randomized to methylphenidate (MPH, long-release capsule, doses 18-36-54mg) versus lisdexamphetamine (LDX, 30-50-70mg). Pharmacotherapy will continue for 6 months before switching to alternative medication. Throughout the Trial, the participants will be evaluated every three months by their diabetologist and online psychological assessments. The primary endpoint (ADHD symptom severity, Conners 3.0 questionnaire) will be assessed by a blinded investigator. Secondary endpoints will include HbA1c, CGM indices, and Quality of Life (PedsQL).

Ethics and dissemination

The trial is approved by Bioethical Committee at Medical University of Lodz and Polish regulatory agency (RNN/142/22/KE, UR/DBL/D/263/2022). The results will be communicated to the research and clinical community, and to Polish agencies responsible for healthcare policy. Patient organizations focused on pediatric T1D will be notified by a consortium member. We hope to utilize the trial`s results to promote collaboration between mental health professionals and diabetes teams, evaluate the economic feasibility of using LDX in patients with both diseases and in the long run improve ADHD treatment in children with T1D.

Strengths and limitations of this study

Strengths:

- Blinded assessment of primary endpoint, use of structured and validated questionnaires for diagnosis and assessment.
- Direct comparison of drugs via cross-over design with planned dose-optimization protocol.

Limitations:

- Patients and physicians not blinded to the drug, possible expectation bias.
- A moderate risk of selection bias – exclusion of patients with more complex psychiatric phenotypes. Caregivers and patients reluctant to stimulant medication drugs may be unwilling to participate.
- Small differences in the efficacy of active compound release between the tested drugs (possible active dose-related bias in clinical effectiveness), dose optimization for LDX not including all market-available intermediate doses.

Keywords:
Attention-deficit hyperactivity disorder, type 1 diabetes, methylphenidate, lisdexamphetamine, clinical trial, HbA1c,

Introduction

ADHD effect on type 1 diabetes treatment

Type 1 diabetes (T1D) is a common disease affecting over one million children worldwide, with an age-standardised incidence of 31/100,000 in Europe, and 16/100,000 in Poland (0-19 years)(1,2).

Recent advantages in medical technology improved glycemic control and significantly reduced rates of diabetes complications(3,4). However, state-of-art therapy of T1D requires frequent blood glucose monitoring, counting of carbohydrates intake and adjustments of administered insulin doses. These and other activities put considerable burden on the patient and their guardians. To benefit from such intensive treatment, a child needs efficient executive functioning and high level of self-control – and those who lack those abilities might face the gap between expected and achieved outcomes.

In particular, comorbid psychological and neurodevelopmental disorders were shown to impair diabetes management(5–8). A prime example is attention deficit hyperactivity disorder (ADHD), which affects 5-10% of children(9) and is reported to be up to 35% more frequent (OR 1.35; 95% CI: 1.08–1.73) in patients with T1D compared to healthy peers(10). A Swedish active screening of children with T1D showed that among children with newly diagnosed ADHD, 77.8% had inadequate metabolic control (mean HbA1c>8.6%) compared to 42.9% in the group of children with treated ADHD(11). Association between ADHD and poor T1D control were also reported by German and Israeli studies(12,13). In addition, those patients experience an elevated risk of life-threatening episodes of severe hypoglycemia or ketoacidosis, resulting in prolonged hospitalizations(10,14,15) and long-term complications, such as diabetic nephropathy(5). In that perspective the need for evidence regarding the effectiveness and safety of ADHD treatment in pediatric T1D emerges as a pertinent clinical challenge.

Current ADHD treatments and their effects on type 1 diabetes

No randomized clinical trials (RCT) have been conducted regarding the effectiveness and safety of ADHD treatment in those with coexisting T1D. Therefore, despite the tremendous impact that both conditions have on patients' everyday life, current clinical guidelines on the psychological management of T1D do not address the problem of ADHD(16).

Many European therapeutic guidelines recommend environmental modifications or psychosocial intervention as first-line treatment for children with ADHD(17–19). Parent training in behavior management (PT) is a psychosocial intervention aimed at improving caregiver's understanding of ADHD symptoms and helping them acquire skills to deal with everyday challenging behavior and support child development. Although PT improves parenting and reduces conduct problems, meta-analyses found no effect of PT on core ADHD symptoms when raters were blinded to the treatment allocations(20). If, despite PT, symptoms of ADHD persist and cause significant impairment of everyday functioning, pharmacotherapy is recommended.

Preferred medications include stimulants, which showed better efficacy (higher effect sizes) on ADHD core symptom reduction and easier dose optimization protocols than non-psychostimulating medications(21,22). Two psychostimulants with best evidence for effectiveness and tolerability are methylphenidate (MPH) and lisdexamphetamine (LDX). LDX, contrary to MPH, is an inactive prodrug that requires enzymatic conversion, resulting in an extended and more stable acting time (~13h). In most international guidelines, LDX is advised as first line treatment comparable to long-acting MPH, or as a secondary drug after treatment failure with previous MPH medication attempts(22). In Poland LDX is neither reimbursed by the National Health Fund (NHF) nor commercially available. As a result, long-acting MPH formulations are considered the first-line pharmacotherapy for ADHD(23).

Limited retrospective data demonstrates that patients with ADHD and T1D treated with stimulants show lower HbA1c (8.1±1.0%) compared to children that were diagnosed but not treated pharmacologically (8.5±1.1%)(24). At the same time, others reported higher blood pressure and no difference in metabolic control(12,13). However, generalization of those results remains limited due to the low sample size, lack of evidence from RCTs, and no direct comparisons between LDX and MPH. In conclusion, there is a lack of data on the safety and effectiveness of ADHD medication in children with T1D regarding the effect on ADHD symptoms, quality of life, and metabolic control.

The aim of the Study

The Trial aims to compare the safety and efficacy of ADHD treatment with LDX or MPH in children and adolescents with ADHD and T1D.

Methods and analysis

Study design and population

LAMAinDiab is a phase 2 randomized cross-over openlabel clinical trial with blinded endpoint assessment. Cross-over design was chosen based on the sample size analysis, as well as for ethical reasons – to provide each participant with an active drug with proven efficacy in ADHD. The project is funded by the Medical Research Agency (pol. “Agencja Badań Medycznych”), which supports non-commercial clinical trials in Poland through open calls. Upon grant application, the project consortium was established, and four recruiting sites – that collectively provide care for ~25% of national pediatric population with T1D(25,26) – were declared.

Patient and Public Involvement statement

The project was consulted with and supported by a national patient organization (Polish Federation for Support of Children and Adolescents with Diabetes, “Diabetycy.eu”), which entered the project`s consortium. Clinical trial`s design and protocol were thoroughly consulted with the organization, and its representative (MZ) was included among the authors to acknowledge her input. Subsequently, the organization`s qualified representatives agreed to play the roles of independent investigators blinded to the treatment allocation and perform ADHD symptom assessments for participating children.

Inclusion and exclusion criteria

Principal inclusion criteria:

- Age 8-16.5 years at trial entry;
- T1D diagnosed according to National and International Guidelines(27),(28) at least 12 months before recruitment, treated with functional intensive insulin therapy,
- ADHD diagnosis according to 5th Edition Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(29) or International Statistical Classification of Diseases (ICD-10)(30) and confirmed as consistent with DSM-5 by a psychiatrist;
- Polish citizenship and health insurance.

Principal exclusion criteria:

- Clinical partial remission of T1D (daily insulin dose<0.3 units per kilogram and concomitant HbA1c measurement ≤6.5% from the last 3 months) or severely unsatisfactory glycemic control (mean HbA1c over the past year ≥12%, excluding HbA1c measurement at T1D diagnosis);
- Clinically apparent or previously-diagnosed cardiovascular disease: hemodynamically significant heart defect, advanced vascular atherosclerosis, or documented hypertension (at least stage 2);
- Diagnosed intellectual disability or other disability that prevents patient adherence to the therapeutic regimen; history of other mental illness or disorder preventing participation in the trial, e.g. bipolar disorder, schizophrenia, other psychotic disorders, history of suicide attempts or present suicide intentions, psychoactive substances abuse;
- Contraindications to either studied drug.
- Language barrier making it impossible to conduct a full psychological consultation in Polish, lack of permanent residence and national insurance in Poland;
- Inability of the parents/legal guardians' to come to the Centre at the time specified by the protocol, in particular – to pick up the study drugs at the dose adjustment stage (the need to pick up 4-5 times over 6-8 weeks, each time within 2-3 days of receiving the recommendations);
- Other reasons that, in the opinion of the attending physician, are more likely to result in difficulties in maintaining the participant's participation in the trial or harm to the participant's health in case of participation in the trial.

Setting

The Trial will be conducted in 4 pediatric diabetology centres, and apply telemedical tools to facilitate recruitment, improve compliance and reduce the burden on participants and their families. The participating centres provide coordinated pediatric diabetes care for their respective voivodeships (regions of Poland):

- Lodzkie voivodeship: Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Pediatric Centre of the Central Clinical Hospital of the Medical University of Lodz;
- Silesian voivodeship: Department of Children's Diabetology, Medical University of Silesia, Upper Silesian John Paul II Child Health Centre;

- Pomeranian voivodeship: Department of Pediatrics, Diabetology, and Endocrinology of the Medical University of Gdansk, University Clinical Centre in Gdansk;
- Opole voivodeship: Department of Pediatrics of the Institute of Medical Sciences of the University of Opole (Department of Pediatrics and the Diabetology Clinic for Children of the University Clinical Hospital in Opole).

Information about the centres was published on the project's website - lamaindiab.umed.pl. Pediatric diabetology centres included in the trial are public care providers – the trial visits and procedures will be carried out as add-ons to routine visits related to the management of diabetes. Pediatric healthcare in Poland is tax-financed by the National Health Found (NHF) and provides universal, free-of-charge care for all children registered in Poland and their caregivers.

Summary of trial procedures

Patients with ADHD and T1D, meeting the clinical trial's inclusion criteria may enroll into the Trial in the designated reference centres. First, their guardians will receive information about the study from the centre`s representative via phone, followed by complete Information and Consent forms sent to agreed mail address. During the next routine outpatient consultation, the guardians and children will thoroughly discuss the information provided with an investigator. After answering any questions related to the study and its protocol, the investigator will verify inclusion and exclusion criteria and obtain signed informed consent form in line with current regulations (from both parents and children ≥13y.o.). After successful recruitment, study procedures will be initiated. Simplified patient's course in the clinical trial is demonstrated in Figure 1.

[FIGURE 1]

Each patient will begin the Trial starting with the enrollment appointment, followed by a baseline assessment by a diabetologist and a psychological evaluation. At this stage, all trial participants will be provided with the following devices: pre-configured tablets with appropriate telecommunication software and prepaid internet access, wrist accelerometers, and blood pressure monitors. All devices will be provided by the Medical University of Lodz to assist participants and their parents in following the study procedures and data collection. Additionally, willing patients who did not qualify for reimbursement will be provided with continuous glucose monitoring (CGM) sensors and receivers and instructed in their use.

Next, the patient's parents/legal guardians will participate in a PT program of 10 themed online workshops (90 minutes long) led by psychotherapists and supplemented with homework and educational materials. PT aims to provide immediate educational and behavioral support for the child's caretakers by educating them about ADHD and providing tools and skills to understand and modify the child's behaviors and was demonstrated to strengthen family bonds and improve adherence to future pharmacotherapy. To successfully complete this phase of the Trial, participant's guardians must participate in at least 8 meetings – with a possible revisit of the missed ones in another cycle.

After completion of PT, each participant will repeat the psychological evaluation to assess the effects of PT intervention alone on ADHD symptoms severity. Those with sustained clinically-significant ADHD symptoms will be qualified for pharmacological intervention. Possible

contraindications for pharmacotherapy will be assessed during the next diabetological visit. The add-on procedures will include urine tests (pregnancy and panel test for substance use), ECG with QT segment assessment (to exclude long QT syndrome) and ophthalmological consultation (to exclude glaucoma). Subsequent and final assessment and qualification will be performed by psychiatrist during an online consultation. Afterward, each participant starting pharmacotherapy will be randomized using a digital randomization system to receive either MPH or LDX as the first drug.

The dose will be optimized during up to four biweekly psychiatric consultations in a flexible manner (allowing both one-step increase and decrease between set minimum and maximum dose for each studied drug). After the maximum tolerated dose is established, patients will continue pharmacotherapy for 6 months. During that time, treatment safety and efficacy will be evaluated twice - after first 3 months by psychological and diabetes care team's evaluation (with small dose adjustments allowed) and after full course (6 months) of therapy. On-demand psychiatric consultations will be allowed. In addition, during both diabetological visits each participant will donate a dry blood sample for evaluation of the concentration of an allocated drug, and another sample will be self-collected on the day of the final psychological assessment for that arm to ensure that endpoint measurements are not biased by incidental non-adherence. After the last evaluation, participants will return the unused drug to their diabetes care centre and will begin a wash-out period.

Qualification for the second arm of pharmacotherapy will be based on the same procedures and consultations which will be performed in parallel with the last diabetological assessment in the first arm. Final switch and start of the second drug (LDX or MPH) will be based on psychiatrist decision. Dose adjustment, safety and efficacy monitoring will follow the same procedures over the next 6 months. Schedule of the Trial's procedures was presented in Supplementary Table 1.

At the end of patient's participation in the Trial, all the devices will be returned to the University, and the last safety and efficacy interview will be performed. All the patients will receive further treatment recommendations at NHF facilities.

Randomization

The starting drug will be determined using block randomization stratified by the trial centre in a 1:1 ratio between MPH and LDX. The risk of randomization error will be minimized by using a user-friendly "Randomizer" IT tool provided by the Sponsor, integrated with the eCRF. In the event of unexpected randomization difficulties (e.g., lack of internet access or other technical problems), centre's trial-coordinator may request randomization via backup randomization list available only for sponsor's representative, re-randomization or patient's withdrawal.

Blinding

The participant allocation is open both to the participant and their guardians as well as their attending physician (diabetologist and psychiatrist alike). Blinding at participant level was considered but decided against due to practical reasons (i.e. costs and difficulties in producing effective over-encapsulation, high risk for spontaneous unblinding due to differences in pharmacokinetics of the studied drugs). However, the people assessing the primary outcome

(i.e. ADHD symptom severity) will be blinded to the allocation and operating independently from the care centres. No exceptions or unblinding options are planned for those researchers as their assessment serves mostly research purpose, and data collected by them are reviewed by unblinded clinicians.

Endpoints and analysis

The **primary endpoints** of the Trial are:

1. Efficacy, defined as change in the severity of ADHD symptoms ("inattention" and "hyperactivity/impulsivity" measured by Conners 3 questionnaire) compared between LDX vs. MPH.
2. Safety, defined as frequency of MedDRA-defined adverse events for both drugs.

For each participant, we will calculate the difference in questionnaire scores ("inattention" and "hyperactivity/impulsivity") at the end of each arm versus the initiation of drug therapy (before first drug). Separate comparisons will be made for each subscale and informant (guardian/child).

Safety analysis will report the number of recorded events by type and severity and the incidence rate (the number of events divided by the number of patient-months of observation).

The **secondary endpoints** of the Trial are (all compared between LDX and MPH arms):

1. Diabetes control, as measured by HbA1c and CGM-derived time in target range, mean sensor glucose, and coefficient of variation, before and after treatment with each of investigated drugs;
2. General and diabetes-related quality of life (measured with PedsQL questionnaires), before and after treatment with each of investigated drugs;
3. Number and percentage of trial participants that achieved improvement of ADHD symptoms (Conners 3 "inattention" and "hyperactivity/impulsivity") defined as 33% reduction in scale values compared to baseline.

The **exploratory endpoints** of the Trial are:

1. Difference between LDX vs. MPH in school attendance during the month preceding the 6-month drug evaluation;
2. Difference between LDX vs. MPH in physical activity (daily steps, % of time in moderate-to-vigorous physical activity) and sleep (duration, latency, efficiency) indices;
3. Differences between baseline assessment and after PT completion concerning: in ADHD symptoms severity (Conners 3 "inattention" and "hyperactivity/impulsivity"), HbA1c and CGM-derived glycemic control (time in range, mean sensor glucose, coefficient of variation);
4. Difference between LDX vs. MPH in frequency (number of events per patient-months) of acute diabetes complications (severe hypoglycemia, ketoacidosis) and hospitalizations, and number of days spent in inpatient care (number of days per patient-months).

Tools and parameters used during the Trial

During in-patient visits in the Trial, standard procedures will be performed, including anthropometric, heart rate, and blood pressure measurements. Applicable values will be referenced with Polish percentile charts.

ADHD symptoms will be measured using The Conners' Rating Scales (The Conners 3.0 scales, Polish version) completed by parents (Conners 3.0-P) and children (Conners 3.0-SR). The Conners' Rating Scales are validated and most commonly used tools to assess difficulties in children and adolescents with ADHD in research and clinical settings worldwide. The Polish version of Conners 3.0 has proven high psychometric reliability and validity. In the Trial, we will focus on changes in content scales of "Inattention" and "Hyperactivity/Impulsivity", two core domains of ADHD symptoms by DSM-5(29).

Diabetes control will be assessed using HbA1c measured in local laboratories using methods concordant with the NGSP program. Moreover, patients will be instructed to use continuous glucose monitoring (CGM) according to their leading physicians' recommendations and generated data will be collected during diabetes check-ups. In Poland, CGM is reimbursed in the form of intermittently-scanned CGM, with possible extension into real-time CGM for those with impaired awareness of hypoglycemia. If available, CGMs will be linked with appropriate devices: insulin pumps, CGM readers, mobile phones. CGM data will be backed up and processed using GlyCulator 3.0 platform(31). For wrist accelerometer data, manufacturer-provided software will be used to collect the data for further analysis.

Patient's quality-of-life (QoL) will be measured using the Pediatric Quality of Life Inventory 3.2 Core (PedsQL QoL) and Diabetes Module (PedsQL diab)(32). The PedsQL is the most common tool to measure QoL in the pediatric population. The PedsQL Diabetes Module allows focusing on T1D-specific issues, especially relevant for the ADHD interaction with T1D self-control. PedsQL QoL and diab have been translated into Polish and validated for academic and commercial use.

During the drug dose-optimization period, patients will be tasked with performing self-assessment, including self-monitoring of blood pressure using automated monitors, diabetes monitoring with CGM, and activity monitoring using a wrist accelerometer. Blood pressure monitors data will be periodically uploaded into a central data repository integrated with electronic case report forms (eCRF), while wrist accelerometry will be stored and analysed at the Trial completion. CGM data will be backed up on in-patient clinic visits using appropriate software in each centre.

Statistical analysis

The primary outcome will be compared between the LDX and MPH group using paired t-tests and multivariable regression models to account for clinical covariates. Sensitivity analysis will be performed for primary and secondary endpoints for the subgroup of patients with no imputed data.

For each intervention, the % of reported adverse events will be reported with the relevant statistics for paired comparisons (Chi2, p), and for the entire table (T_{MB}, p).The incidence rates for individual adverse events will be compared with appropriate statistical tests (Poisson test

or equivalent). In addition, each type of event will be compared using the McNemar test, and the frequencies of different events using the McNemar-Bowker global symmetry test.

Treatment safety will be assessed and reported following standard procedures and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and WHO severity scale, and recorded in eCRF.

Safety and efficacy endpoints will be analysed using data from patients who completed both planned treatments, independent of potential protocol deviations (i.e., population "as treated"). Data of patients lost to follow-up will be filled in on the basis of last-observation carried forward, provided that they have at least one complete timepoint of outcome measures on the current treatment. Patients with deviations from protocol leading to no outcome data will not be included in efficacy analyses.

The secondary and exploratory endpoints will be evaluated using the appropriate statistical methods for either continuous (paired t-test, linear regression) or nominal variables (McNemar test). Interim analyses were not planned within this study.

Sample size estimation

To our knowledge, at the time of planning this Trial, no trial with equivalent design and outcome measures in this population was published. Thus, we calculated the sample size to allow for detection of a moderate difference (0.33 standard deviations) difference in score changes between LDX vs. MPH for the key Conners 3 measures(33). Such difference was deemed clinically-impactful by the clinical team designing the trial. To estimate the sample size, we assumed significance threshold of alpha=0.05, the statistical power of 80%. The risk of applying multiple tests (each scale in each type of responder – four in total) was assessed as minimal due to high intercorrelations among those measures. As such, no alpha adjustment was planned. Such assumptions yielded the minimum number of participants of 89 (rounded to 90). The risk of drop-out during pharmacotherapy was assessed as considerable (~33%) due to the challenging population of interest (children with ADHD and T1D, with ADHD possibly present in parents) and known side effects of tested medications. Thus, the target number of pharmacologically-treated children was planned at 135, and 150 recruited given that up to 10% might be disqualified from pharmacotherapy due to drug contraindications or considerable improvement after PT. Assuming recruitment success at 80% (considerable benefit for patients, access to a drug unavailable in Poland, coordinated diabetes and psychiatric care), we estimated that 190 children that should be approached. Based on the general prevalence of ADHD in the pediatric population, the number of patients with T1D to screen for ADHD would be at least 4000 – which was a number of patients supervised by the 4 Trial centres.

Data entry and storage

Patient data collected during the clinical Trial will be stored within the electronic trial documentation database, following appropriate regulations, with data access provided to appropriate trial personnel. Reported, presented, and published data will be anonymized. The clinical trial records will be stored for 25 years after trial completion.

Trial monitoring

Trial monitoring will follow adequate international and national clinical trial regulations. Sponsor's representatives will visit each site, discuss the clinical trial course, review and validate relevant records, and verify all reference centres' that partake in the clinical trial. National regulatory authorities may request access to research documentation, source documents, research personnel, and facilities. The Sponsor will be notified of any centre's audits by regulatory agencies, and copies of audit reports will be transferred accordingly.

Trial timeline

Planned date for starting the study is 1.01.2024, but may be prone to change following logistic reasons. The trial is planned to last 48 months, setting the tentative end date of the study at 1.12.2027.

Ethics and dissemination

Ethical considerations

The clinical trial follows principles of the Helsinki Declaration, current Good Clinical Practice guidelines, and other applicable regulations. The clinical trial has been registered in European Union Drug Regulating Authorities Clinical Trials Database (no. 2022-001906-24) and in ClinicalTrials.gov (NCT05957055). The clinical trial was approved by the Bioethical Committee at Medical University of Lodz (agreement no. RNN/142/22/KE), and the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (UR/DBL/D/263/2022). All participants of the clinical trial are insured within the appropriate insurance agreements (policy no. COR233280) and signed informed consent forms from them and their parents will be collected before trial procedures. All changes in the Trial are subject to ethical and regulatory review before their incorporation into the clinical trial.

Safety during and post intervention

Before the intervention, the treatment of coexisting diseases will be recorded in the eCRF and continued as is or appropriately modified by the respective specialist. All adverse events will be documented in the electronic trial documentation using MedDRA v24.1 and graded using applicable WHO standards, with SAE reported within 24 hours since the occurrence and evaluated by Safety Monitoring Team (SMT). In case of a SUSAR, the SMT follows the Council for International Organizations of Medical Sciences forms and reports it to appropriate authorities within 15 days (or 7 in case of threat to the life or death of the patient) from receiving the report, following the data transfer procedure with the applicable law. The SMT will provide an annual patient safety report throughout the clinical trial, including appropriate information on treatment safety. The Sponsor holds the right to pause or discontinue part of the trial, the entire trial, or the participation of an individual patient.

After trial completion, all the patients will receive further treatment instructions, prescription for ADHD treatment and referral to appropriate health provider facilities. Reference diabetology centres will provide continued diabetes care under NHF.

Dissemination plan

Results will be submitted for publication in leading international scientific journals in diabetes care, endocrinology and psychiatry. Results will also be shared during relevant national and international congresses and conferences. The cooperation between the Sponsor and patient organization (affiliation 13) will be continued after the Trial's completion to increase awareness of the impact of psychiatric diseases in patients with T1D. The study`s results will also be communicated to the funding agency and national healthcare policy makers.

Discussion

Despite the favorable opinion of the Polish Agency for Health Technology Assessment and Tariff System, LDX is still unavailable for Polish patients outside this clinical trial. We will provide data collected during this Trial for consideration of the Agency, to promote discussion about the availability of LDX and advocate for it being widely accessible (if not reimbursed). We will also perform a specific cost-effectiveness analysis for the particular population of children with ADHD and T1D, and investigate possible costs and benefits of considering LDX as a first-line treatment in this group of patients, justified by the system savings provided by possibly-improved diabetes control.

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Author contribution: AM, JC, HKK, WF, AB, KB – written the article, prepared the clinical trial protocol; WF, AB, AM, KB – supervised the clinical trial registration; EK – translated the clinical trial protocol and written the supplementary materials; BM, ASz, ACh, PJCh, MM, IM, AK, TW, WF, AB – consulted the manuscript and the clinical trial protocol; MZ –supervised patients consultation of the clinical trial. All authors reviewed the results and approved the final version of the manuscript. We comply to the ICMJE guidelines.

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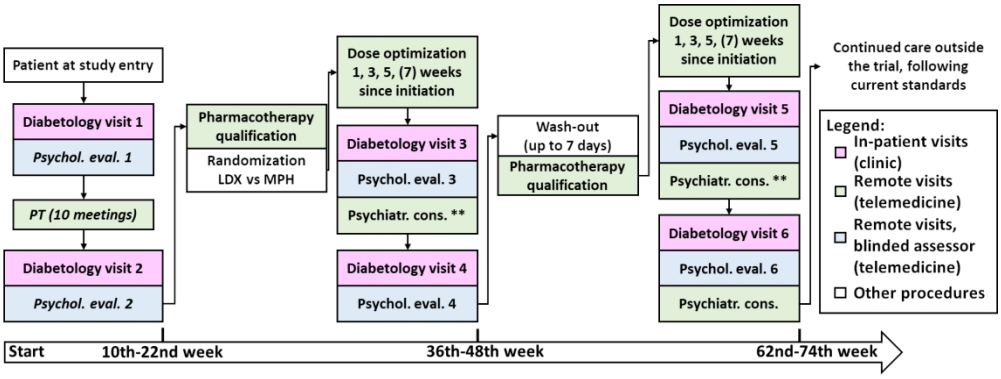

Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH – methylphenidate. ** - if needed on-demand consultation

315x117mm (150 x 150 DPI)

Supplementary Table 1. Study schedule. The order of treatment (A/B) will be decided at randomization (allocation step). Names of visits corresponding to Figure 1 are included.

			STUDY PERIOD									
			Enroll	PT	Allocate	Post-allocation						
	DURATION		*1 week*	*10-22 weeks*	*1 week*	*First treatment (6 months)*			*Second treatment (6 months)*			
ENROLLMENT	Eligibility screen		X		X			X				
	Informed consent		X									
	Randomization (to A/B)				X							
INTERVENTION	Parent training in behaviour management			X								
	Cross-over	MPH				A	A	A	B	B	B	
		LDX				B	B	B	A	A	A	
ASSESSMENTS	Conners 3, PedsQL questionnaires		Psychological evaluatlion 1		Psychological evaluation 2		Psychological evaluation 3	Psychological evaluaton 4		Psychological evaluaton 5	Psychological evaluaton 6	
	Diabetes control (HbA1c, CGM)		Diabetological visit 1		Diabetological visit 2		Diabetological visit 3	Diabetological visit 4		Diabetological visit 5	Diabetological visit 6	
	Anthropometric, BP, HR measruement											
	Urine tests, ECG with QT segment assessment, ophthalmologic consultation											
	Psychiatric consultation				LDX/MPH qualification	Dose optimization	*Additional dose adjustment		Dose optimization	*Additional dose adjustment	Referral to care under National Health Fund	

*optional, up to the Investigator, only lowering of dose allowed

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1-4**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**S2: 5-8** **S2: 10**
	2b	All items from the World Health Organization Trial Registration Data Set	**S2: 4-150**
Protocol version	3	Date and version identifier	**S2: 3**
Funding	4	Sources and types of financial, material, and other support	**569-570**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**5-8** **563-568**
	5b	Name and contact information for the trial sponsor	**S2: 14** **S2: 16-19**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**151-156** **229-232** **271-272** **277-281** **570-571** **S2: 152-166**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee)	**S2: 167-201**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the Trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**87-144** **S1: 58-121** **S1: 299-410** **S1: 637-673** **S1: 885-897** **S1: 944-983**
	6b	Explanation for choice of comparators	**323-355**
Objectives	7	Specific objectives or hypotheses	**145-148** **289-322**
Trial design	8	Description of trial design including type of Trial (eg, parallel group, cross-over, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**151-152** **250-252** **S2: 98-99**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**195-215**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**167-196**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**216-273** **S2: 28-32**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**166-194** **253-269** **433-434** **S2: 311-382** **S2: 515-517** **S2: 752-757**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**258-263** **441-443** **S2: 142-147**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the Trial	**424-425**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	**289-355** **S2: 103-142**

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**Figure 1 Table 1 224-273**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**378-398 S2: 101**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**151-156 158-164 196-226 387-398**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**274-281**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**274-281**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**274-281**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**282-288 S2: 28-32 S2: 103-142 S2: 179-182**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the Trial	**282-288**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**289-323 323-355 S2: 122-298 S2: 420-431 S2: 438-458 S2: 674-884 S2: 983-1195**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**237-242 369-374**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**399-403 S2: 174-150 S2: 183-188**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**356-377**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**356-377**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**369-374**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**S2: 167-201**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the Trial	**423-434**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**425-434**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**404-410**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**416-418 S2: 143-144**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**420-422**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**218-225** **S1: 509-537** **S1: 1226-1259**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**218-225** **S1: 412-419** **S1: 476-484** **S1: 898-903** **S1: 1214-1221**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the Trial	**286-288** **334-355** **366-368** **399-403** **424-433** **S1: 491-503** **S1: 538-600** **S1: 892-897** **S1: 1261-1322** **S2: 147-150**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall Trial and each study site	**571**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**405-410** **424-433** **S2: 183-188**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**438-443** **S1: 223-225**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**437-442** **S1: 51-57** **S1: 380-382** **S1: 470-475** **S1: 1209-1213**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**564-569**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**439-443** **S1: 491-503** **S1: 538-600** **S1: 892-897** **S1: 1261-1322**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**S1: 30-601** **S1: 616-906** **S1: 922-1322**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current Trial and for future use in ancillary studies, if applicable	**S1: 412-419** **S1: 476-484** **S1: 898-903** **S1: 1214-1221**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

BMJ Open

LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting

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Primary Subject Heading:	Paediatrics
Secondary Subject Heading:	Diabetes and endocrinology, Mental health
Keywords:	Behavior, Protocols & guidelines < HEALTH SERVICES ADMINISTRATION & MANAGEMENT, Paediatric endocrinology < DIABETES & ENDOCRINOLOGY, Child & adolescent psychiatry < PSYCHIATRY, Randomized Controlled Trial, Impulse control disorders < PSYCHIATRY

Title: LisdexAmphetamine versus Methylphenidate for Pediatric Patients with Attention-Deficit Hyperactivity Disorder and Type 1 Diabetes (LAMAinDiab) – protocol for a multicentre, randomized cross-over clinical trial in an outpatient telemedicine-supported setting

Authors: Arkadiusz Michalak*[1-3], Jędrzej Chrzanowski*[1], Hanna Kuśmierczyk-Kozieł[2], Ewa Klejman[1], Katarzyna Błaziak[3], Beata Mianowska[2], Agnieszka Szadkowska[2], Agata Chobot[4,5], Przemysława Jarosz-Chobot[6], Małgorzata Myśliwiec[7], Iwona Makowska[8,9], Anna Kalenik[10], Monika Zamarlik[11,12], Tomasz Wolańczyk[10], Wojciech Fendler[1,3,13], Agnieszka Butwicka[1, 14,15,16]

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Word count: 4105/4000

ABSTRACT

Introduction

Attention deficit hyperactivity disorder (ADHD) affects 5-10% of pediatric population and is reportedly more common in children with type 1 diabetes (T1D), exacerbating its clinical course. Proper treatment of ADHD in such patients may thus provide neurological and metabolic benefita . To test this, we designed a non-commercial 2nd phase clinical trial comparing the impact of different pharmacological interventions for ADHD in children with T1D.

Methods and analysis

This is a multicentre, randomized, open-label, cross-over clinical trial in children and adolescents with ADHD and T1D. The Trial will be conducted in four reference pediatric diabetes centres in Poland. Over 36 months, eligible patients with both T1D and ADHD (aged 8-16.5 years, T1D duration >1 year) will be offered participation. Patients`s guardians will undergo online once-weekly training sessions behavior management for ten weeks. Afterward, children will be randomized to methylphenidate (MPH, long-release capsule, doses 18-36-54mg) versus lisdexamphetamine (LDX, 30-50-70mg). Pharmacotherapy will continue for 6 months before switching to alternative medication. Throughout the Trial, the participants will be evaluated every three months by their diabetologist and online psychological assessments. The primary endpoint (ADHD symptom severity, Conners 3.0 questionnaire) will be assessed by a blinded investigator. Secondary endpoints will include HbA1c, CGM indices, and Quality of Life (PedsQL).

Ethics and dissemination

The trial is approved by Bioethical Committee at Medical University of Lodz and Polish regulatory agency (RNN/142/22/KE, UR/DBL/D/263/2022). The results will be communicated to the research and clinical community, and to Polish agencies responsible for healthcare policy. Patient organizations focused on pediatric T1D will be notified by a consortium member. We hope to utilize the trial`s results to promote collaboration between mental health professionals and diabetes teams, evaluate the economic feasibility of using LDX in patients with both diseases and in the long run improve ADHD treatment in children with T1D.

Strengths and limitations of this study

Strengths:

- Blinded assessment of primary endpoint, use of structured and validated questionnaires for diagnosis and assessment.
- Direct comparison of drugs via cross-over design with planned dose-optimization protocol.

Limitations:

- Patients and physicians not blinded to the drug, possible expectation bias.
- A moderate risk of selection bias – exclusion of patients with more complex psychiatric phenotypes. Caregivers and patients reluctant to stimulant medication drugs may be unwilling to participate.
- Small differences in the efficacy of active compound release between the tested drugs (possible active dose-related bias in clinical effectiveness), dose optimization for LDX not including all market-available intermediate doses.

Keywords:
Attention-deficit hyperactivity disorder, type 1 diabetes, methylphenidate, lisdexamphetamine, clinical trial, HbA1c,

Introduction

ADHD effect on type 1 diabetes treatment

Type 1 diabetes (T1D) is a common disease affecting over one million children worldwide, with an age-standardised incidence of 31/100,000 in Europe, and 16/100,000 in Poland (0-19 years)(1,2).

Recent advantages in medical technology improved glycemic control and significantly reduced rates of diabetes complications(3,4). However, state-of-art therapy of T1D requires frequent blood glucose monitoring, counting of carbohydrates intake and adjustments of administered insulin doses. These and other activities put considerable burden on the patient and their guardians. To benefit from such intensive treatment, a child needs efficient executive functioning and high level of self-control – and those who lack those abilities might face the gap between expected and achieved outcomes.

In particular, comorbid psychological and neurodevelopmental disorders were shown to impair diabetes management(5–8). A prime example is attention deficit hyperactivity disorder (ADHD), which affects 5-10% of children(9) and is reported to be up to 35% more frequent (OR 1.35; 95% CI: 1.08–1.73) in patients with T1D compared to healthy peers(10). A Swedish active screening of children with T1D showed that among children with newly diagnosed ADHD, 77.8% had inadequate metabolic control (mean HbA1c>8.6%) compared to 42.9% in the group of children with treated ADHD(11). Association between ADHD and poor T1D control were also reported by German and Israeli studies(12,13). In addition, those patients experience an elevated risk of life-threatening episodes of severe hypoglycemia or ketoacidosis, resulting in prolonged hospitalizations(10,14,15) and long-term complications, such as diabetic nephropathy(5). In that perspective the need for evidence regarding the effectiveness and safety of ADHD treatment in pediatric T1D emerges as a pertinent clinical challenge.

Current ADHD treatments and their effects on type 1 diabetes

No randomized clinical trials (RCT) have been conducted regarding the effectiveness and safety of ADHD treatment in those with coexisting T1D. Therefore, despite the tremendous impact that both conditions have on patients' everyday life, current clinical guidelines on the psychological management of T1D do not address the problem of ADHD(16).

Many European therapeutic guidelines recommend environmental modifications or psychosocial intervention as first-line treatment for children with ADHD(17–19). Parent training in behavior management (PT) is a psychosocial intervention aimed at improving caregiver's understanding of ADHD symptoms and helping them acquire skills to deal with everyday challenging behavior and support child development. Although PT improves parenting and reduces conduct problems, meta-analyses found no effect of PT on core ADHD symptoms when raters were blinded to the treatment allocations(20). If, despite PT, symptoms of ADHD persist and cause significant impairment of everyday functioning, pharmacotherapy is recommended.

Preferred medications include stimulants, which showed better efficacy (higher effect sizes) on ADHD core symptom reduction and easier dose optimization protocols than non-psychostimulating medications(21,22). Two psychostimulants with best evidence for effectiveness and tolerability are methylphenidate (MPH) and lisdexamphetamine (LDX). LDX, contrary to MPH, is an inactive prodrug that requires enzymatic conversion, resulting in an extended and more stable acting time (~13h). In most international guidelines, LDX is advised as first line treatment comparable to long-acting MPH, or as a secondary drug after treatment failure with previous MPH medication attempts(22). In Poland LDX is neither reimbursed by the National Health Fund (NHF) nor commercially available. As a result, long-acting MPH formulations are considered the first-line pharmacotherapy for ADHD(23).

Limited retrospective data demonstrates that patients with ADHD and T1D treated with stimulants show lower HbA1c (8.1±1.0%) compared to children that were diagnosed but not treated pharmacologically (8.5±1.1%)(24). At the same time, others reported higher blood pressure and no difference in metabolic control(12,13). However, generalization of those results remains limited due to the low sample size, lack of evidence from RCTs, and no direct comparisons between LDX and MPH. In conclusion, there is a lack of data on the safety and effectiveness of ADHD medication in children with T1D regarding the effect on ADHD symptoms, quality of life, and metabolic control.

The aim of the Study

The Trial aims to compare the safety and efficacy of ADHD treatment with LDX or MPH in children and adolescents with ADHD and T1D.

Methods and analysis

Study design and population

LAMAinDiab is a 2nd phase randomized cross-over open label clinical trial with blinded endpoint assessment. Cross-over design was chosen based on the sample size analysis, as well as for ethical reasons – to provide each participant with an active drug with proven efficacy in ADHD. The project is funded by the Medical Research Agency (pol. “Agencja Badań Medycznych”), which supports non-commercial clinical trials in Poland through open calls. Upon grant application, the project consortium was established, and four recruiting sites – that collectively provide care for ~25% of national pediatric population with T1D(25,26) – were declared.

Patient and Public Involvement statement

The project was consulted with and was supported by a national patient organization (Polish Federation for Support of Children and Adolescents with Diabetes, “Diabetycy.eu”), which entered the project`s consortium. Clinical trial`s design and protocol were thoroughly consulted with the organization, and its representative (MZ) was included among the authors to acknowledge her input. Subsequently, the organization`s qualified representatives agreed to play the roles of independent investigators blinded to the treatment allocation and perform ADHD symptom assessments for participating children.

Inclusion and exclusion criteria

Principal inclusion criteria:

- Age 8-16.5 years at trial entry;
- T1D diagnosed according to National and International Guidelines(27)(28) at least 12 months before recruitment, treated with functional intensive insulin therapy,
- ADHD diagnosis according to 5th Edition Diagnostic and Statistical Manual of Mental Disorders (DSM-5)(29) or International Statistical Classification of Diseases (ICD-10)(30) and confirmed as consistent with DSM-5 by a psychiatrist;
- Polish citizenship and health insurance.

Principal exclusion criteria:

- Clinical partial remission of T1D (daily insulin dose<0.3 units per kilogram and concomitant HbA1c measurement ≤6.5% from the last 3 months) or severely unsatisfactory glycemic control (mean HbA1c over the past year ≥12%, excluding HbA1c measurement at T1D diagnosis);
- Clinically apparent or previously-diagnosed cardiovascular disease: hemodynamically significant heart defect, advanced vascular atherosclerosis, or documented hypertension (at least stage 2);
- Diagnosed intellectual disability or other disability that prevents patient adherence to the therapeutic regimen; history of other mental illness or disorder preventing participation in the trial, e.g. bipolar disorder, schizophrenia, other psychotic disorders, history of suicide attempts or present suicide intentions, psychoactive substances abuse;
- Contraindications (in line with product characteristics, described in detail at https://clinicaltrials.gov/study/NCT05957055), allergy or hypersensitivity to either studied drug.
- Language barrier making it impossible to conduct a full psychological consultation in Polish, lack of permanent residence and national insurance in Poland;
- Declared inability or unwillingness of the parents/legal guardians' to come to the Centre at the time specified by the protocol, in particular – to pick up the study drugs at the dose adjustment stage (the need to pick up 4-5 times over 6-8 weeks, each time within 2-3 days of receiving the recommendations);
- Other reasons that, in the opinion of the attending physician, are more likely to result in difficulties in maintaining the participant's participation in the trial or harm to the participant's health in case of participation in the trial.

Setting

The Trial will be conducted in 4 pediatric diabetology centres, and apply telemedical tools to facilitate recruitment, improve compliance and reduce the burden on participants and their families. The participating centres provide coordinated pediatric diabetes care for their respective voivodeships (regions of Poland):

- Lodzkie voivodeship: Department of Pediatrics, Diabetology, Endocrinology and Nephrology, Pediatric Centre of the Central Clinical Hospital of the Medical University of Lodz;

- Silesian voivodeship: Department of Children's Diabetology, Medical University of Silesia, Upper Silesian John Paul II Child Health Centre;
- Pomeranian voivodeship: Department of Pediatrics, Diabetology, and Endocrinology of the Medical University of Gdansk, University Clinical Centre in Gdansk;
- Opole voivodeship: Department of Pediatrics of the Institute of Medical Sciences of the University of Opole (Department of Pediatrics and the Diabetology Clinic for Children of the University Clinical Hospital in Opole).

Information about the centres was published on the project's website - lamaindiab.umed.pl. Pediatric diabetology centres included in the trial are public care providers – the trial visits and procedures will be carried out as add-ons to routine visits related to the management of diabetes. Pediatric healthcare in Poland is tax-financed by the National Health Found (NHF) and provides universal, free-of-charge care for all children registered in Poland and their caregivers.

Summary of trial procedures

Patients with ADHD and T1D, meeting the clinical trial's inclusion criteria may enroll into the Trial in the designated reference centres. First, their guardians will receive information about the study from the centre`s representative via phone, followed by complete Information and Consent forms sent to agreed mail address. During the next routine outpatient consultation, the guardians and children will thoroughly discuss the information provided with an investigator. After answering any questions related to the study and its protocol, the investigator will verify inclusion and exclusion criteria and obtain signed informed consent form in line with current regulations (from both parents and children ≥13y.o.). After successful recruitment, study procedures will be initiated. Simplified patient's course in the clinical trial is demonstrated in Figure 1.

[FIGURE 1]

Each patient will begin the Trial starting with the enrollment appointment, followed by a baseline assessment by a diabetologist and a psychological evaluation. At this stage, all trial participants will be provided with the following devices: pre-configured tablets with appropriate telecommunication software and prepaid internet access, wrist accelerometers, and blood pressure monitors. All devices will be provided by the Medical University of Lodz to assist participants and their parents in following the study procedures and data collection. Additionally, willing patients who did not qualify for reimbursement will be provided with continuous glucose monitoring (CGM) sensors and receivers and instructed in their use.

Next, the patient's parents/legal guardians will participate in a PT program of 10 themed online workshops (once-weekly sessions, 90 minutes long) led by psychotherapists and supplemented with homework and educational materials. PT aims to provide immediate educational and behavioral support for the child's caretakers by educating them about ADHD and providing tools and skills to understand and modify the child's behaviors and was demonstrated to strengthen family bonds and improve adherence to future pharmacotherapy. To successfully complete this part of the Trial, participant's guardians must participate in at least 8 meetings – with a possible revisit of the missed ones in another cycle.

After completion of PT, each participant will repeat the psychological evaluation to assess the effects of PT intervention alone on ADHD symptoms severity. Those with sustained clinically-significant ADHD symptoms will be qualified for pharmacological intervention. Possible contraindications for pharmacotherapy will be assessed during the next diabetological visit. The add-on procedures will include urine tests (pregnancy and panel test for substance use), ECG with QT segment assessment (to exclude long QT syndrome) and ophthalmological consultation (to exclude glaucoma). Subsequent and final assessment and qualification will be performed by psychiatrist during an online consultation. Afterward, each participant starting pharmacotherapy will be randomized using a digital randomization system to receive either MPH or LDX as the first drug.

The dose titration protocol was based on Newcorn et al.(31) flexible-dose design (NCT01552915), with modifications. The dose will be optimized during up to four biweekly psychiatric consultations in a flexible manner (for 5-7 weeks, allowing both one-step increase and decrease between set minimum and maximum dose for each studied drug). After the maximum tolerated dose is established, patients will continue pharmacotherapy for 6 months. During that time, treatment safety and efficacy will be evaluated twice - after first 3 months by psychological and diabetes care team's evaluation (with small dose adjustments allowed) and after full course (6 months) of therapy. On-demand psychiatric consultations will be allowed. In addition, during both diabetological visits each participant will donate a dry blood sample for evaluation of the concentration of an allocated drug, and another sample will be self-collected on the day of the final psychological assessment for that arm to ensure that endpoint measurements are not biased by incidental non-adherence. After the last evaluation, participants will return the unused drug to their diabetes care centre and will begin a wash-out period.

Qualification for the second arm of pharmacotherapy will be based on the same procedures and consultations which will be performed in parallel with the last diabetological assessment in the first arm. Final switch and start of the second drug (LDX or MPH) will be based on psychiatrist decision. Dose adjustment, safety and efficacy monitoring will follow the same procedures over the next 6 months. Schedule of the Trial's procedures was presented in Supplementary Table 1.

At the end of patient's participation in the Trial, all the devices will be returned to the University, and the last safety and efficacy interview will be performed. All the patients will receive further treatment recommendations at NHF facilities.

Randomization

The starting drug will be determined using block randomization stratified by the trial centre in a 1:1 ratio between MPH and LDX. The risk of randomization error will be minimized by using a user-friendly "Randomizer" IT tool provided by the Sponsor, integrated with the eCRF. In the event of unexpected randomization difficulties (e.g., lack of internet access or other technical problems), centre's trial-coordinator may request randomization via backup randomization list available only for sponsor's representative, re-randomization or patient's withdrawal.

Blinding

The participant allocation is open both to the participant and their guardians as well as their attending physician (diabetologist and psychiatrist alike). Blinding at participant level was considered but decided against due to practical reasons (i.e. costs and difficulties in producing effective over-encapsulation, high risk for spontaneous unblinding due to differences in pharmacokinetics of the studied drugs). However, the people assessing the primary outcome (i.e. ADHD symptom severity) will be blinded to the allocation and operating independently from the care centres. No exceptions or unblinding options are planned for those researchers as their assessment serves mostly research purpose, and data collected by them are reviewed by unblinded clinicians.

Endpoints and analysis

The **primary endpoints** of the Trial are:

1. Efficacy, defined as change in the severity of ADHD symptoms ("inattention" and "hyperactivity/impulsivity" measured by Conners 3 questionnaire) compared between LDX vs. MPH.
2. Safety, defined as frequency of MedDRA-defined adverse events for both drugs.

For each participant, we will calculate the difference in questionnaire scores ("inattention" and "hyperactivity/impulsivity") at the end of each arm versus the initiation of drug therapy (before first drug). Separate comparisons will be made for each subscale and informant (guardian/child).

Safety analysis will report the number of recorded events by type and severity and the incidence rate (the number of events divided by the number of patient-months of observation).

The **secondary endpoints** of the Trial are (all compared between LDX and MPH arms):

1. Diabetes control, as measured by HbA1c and CGM-derived time in target range, mean sensor glucose, and coefficient of variation, before and after treatment with each of investigated drugs;
2. General and diabetes-related quality of life (measured with PedsQL questionnaires), before and after treatment with each of investigated drugs;
3. Number and percentage of trial participants that achieved improvement of ADHD symptoms (Conners 3 "inattention" and "hyperactivity/impulsivity") defined as 33% reduction in scale values compared to baseline.

The **exploratory endpoints** of the Trial are:

1. Difference between LDX vs. MPH in school attendance during the month preceding the 6-month drug evaluation;
2. Difference between LDX vs. MPH in physical activity (daily steps, % of time in moderate-to-vigorous physical activity) and sleep (duration, latency, efficiency) indices;
3. Differences between baseline assessment and after PT completion concerning: in ADHD symptoms severity (Conners 3 "inattention" and "hyperactivity/impulsivity"), HbA1c and CGM-derived glycemic control (time in range, mean sensor glucose, coefficient of variation);

4. Difference between LDX vs. MPH in frequency (number of events per patient-months) of acute diabetes complications (severe hypoglycemia, ketoacidosis) and hospitalizations, and number of days spent in inpatient care (number of days per patient-months).

Tools and parameters used during the Trial

During in-patient visits in the Trial, standard procedures will be performed, including anthropometric, heart rate, and blood pressure measurements. Applicable values will be referenced with Polish percentile charts.

ADHD symptoms will be measured using The Conners' Rating Scales (The Conners 3.0 scales, Polish version) completed by parents (Conners 3.0-P) and children (Conners 3.0-SR). The Conners' Rating Scales are validated and most commonly used tools to assess difficulties in children and adolescents with ADHD in research and clinical settings worldwide. The Polish version of Conners 3.0 has proven high psychometric reliability and validity. In the Trial, we will focus on changes in content scales of "Inattention" and "Hyperactivity/Impulsivity", two core domains of ADHD symptoms by DSM-5(29).

Diabetes control will be assessed using HbA1c measured in local laboratories using methods concordant with the NGSP program. Moreover, patients will be instructed to use continuous glucose monitoring (CGM) according to their attending physicians' recommendations and generated data will be collected during diabetes check-ups. In Poland, CGM is reimbursed in the form of intermittently-scanned CGM, with possible extension into real-time CGM for those with impaired awareness of hypoglycemia. If available, CGMs will be linked with appropriate devices: insulin pumps, CGM readers, mobile phones. CGM data will be backed up and processed using GlyCulator 3.0 platform(32). For wrist accelerometer data, manufacturer-provided software will be used to collect the data for further analysis.

Patient's quality-of-life (QoL) will be measured using the Pediatric Quality of Life Inventory 3.2 Core (PedsQL QoL) and Diabetes Module (PedsQL diab)(33). The PedsQL is the most common tool to measure QoL in the pediatric population. The PedsQL Diabetes Module allows focusing on T1D-specific issues, especially relevant for the ADHD interaction with T1D self-control. PedsQL QoL and diab have been translated into Polish and validated for academic and commercial use.

During the drug dose-optimization period, patients will be tasked with performing self-assessment, including self-monitoring of blood pressure using automated monitors, diabetes monitoring with CGM, and activity monitoring using a wrist accelerometer. Blood pressure monitors data will be periodically uploaded into a central data repository integrated with electronic case report forms (eCRF), while wrist accelerometry will be stored and analysed at the Trial completion. CGM data will be backed up on in-patient clinic visits using appropriate software in each centre.

Statistical analysis

The primary outcome will be compared between the LDX and MPH group using paired t-tests and multivariable regression models to account for clinical covariates. Sensitivity analysis will

be performed for primary and secondary endpoints for the subgroup of patients with no imputed data.

For each intervention, the % of reported adverse events will be reported with the relevant statistics for paired comparisons (Chi2, p), and for the entire table (T_{MB}, p).The incidence rates for individual adverse events will be compared with appropriate statistical tests (Poisson test or equivalent). In addition, each type of event will be compared using the McNemar test, and the frequencies of different events using the McNemar-Bowker global symmetry test.

Treatment safety will be assessed and reported following standard procedures and coded using Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 and WHO severity scale, and recorded in eCRF.

Safety and efficacy endpoints will be analysed using data from patients who completed both planned treatments, independent of potential protocol deviations (i.e., population "as treated"). Data of patients lost to follow-up will be filled in on the basis of last-observation carried forward, provided that they have at least one complete timepoint of outcome measures on the current treatment. Patients with deviations from protocol leading to no outcome data will not be included in efficacy analyses.

The secondary and exploratory endpoints will be evaluated using the appropriate statistical methods for either continuous (paired t-test, linear regression) or nominal variables (McNemar test). Interim analyses were not planned within this study.

Sample size estimation

To our knowledge, at the time of planning this Trial, no trial with equivalent design and outcome measures in this population was published. Thus, we calculated the sample size to allow for detection of a moderate difference (0.33 standard deviations) difference in score changes between LDX vs. MPH for the key Conners 3 measures(34). Such difference was deemed clinically-impactful by the clinical team designing the trial. To estimate the sample size, we assumed significance threshold of alpha=0.05, the statistical power of 80%. The risk of applying multiple tests (each scale in each type of responder – four in total) was assessed as minimal due to high intercorrelations among those measures. As such, no alpha adjustment was planned. Such assumptions yielded the minimum number of participants of 89 (rounded to 90). The risk of drop-out during pharmacotherapy was assessed as considerable (~33%) due to the challenging population of interest (children with ADHD and T1D, with ADHD possibly present in parents) and known side effects of tested medications. Thus, the target number of pharmacologically-treated children was planned at 135, and 150 recruited given that up to 10% might be disqualified from pharmacotherapy due to drug contraindications or considerable improvement after PT. Assuming recruitment success at 80% (considerable benefit for patients, access to a drug unavailable in Poland, coordinated diabetes and psychiatric care), we estimated that 190 children that should be approached. Based on the general prevalence of ADHD in the pediatric population, the number of patients with T1D to screen for ADHD would be at least 4000 – which was a number of patients supervised by the 4 Trial centres.

Data entry and storage

Patient data collected during the clinical Trial will be stored within the electronic trial documentation database, following appropriate regulations, with data access provided to appropriate trial personnel. Reported, presented, and published data will be anonymized. The clinical trial records will be stored for 25 years after trial completion.

Trial monitoring

Trial monitoring will follow adequate international and national clinical trial regulations. Sponsor's representatives will visit each site, discuss the clinical trial course, review and validate relevant records, and verify all reference centres' that partake in the clinical trial. National regulatory authorities may request access to research documentation, source documents, research personnel, and facilities. The Sponsor will be notified of any centre's audits by regulatory agencies, and copies of audit reports will be transferred accordingly.

Trial timeline

Planned date for starting the study is 1.01.2024, but may be prone to change following logistic reasons. The trial is planned to last 48 months, setting the tentative end date of the study at 1.12.2027.

Ethics and dissemination

Ethical considerations

The clinical trial follows principles of the Helsinki Declaration, current Good Clinical Practice guidelines, and other applicable regulations. The clinical trial has been registered in European Union Drug Regulating Authorities Clinical Trials Database (no. 2022-001906-24) and in ClinicalTrials.gov (NCT05957055). The clinical trial was approved by the Bioethical Committee at Medical University of Lodz (agreement no. RNN/142/22/KE), and the Polish Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (UR/DBL/D/263/2022). All participants of the clinical trial are insured within the appropriate insurance agreements (policy no. COR233280) and signed informed consent forms from them and their parents will be collected before trial procedures. All changes in the Trial are subject to ethical and regulatory review before their incorporation into the clinical trial.

Safety during and post intervention

Before the intervention, the treatment of coexisting diseases will be recorded in the eCRF and continued as is or appropriately modified by the respective specialist. All adverse events will be documented in the electronic trial documentation using MedDRA v24.1 and graded using applicable WHO standards, with SAE reported within 24 hours since the occurrence and evaluated by Safety Monitoring Team (SMT). In case of a SUSAR, the SMT follows the Council for International Organizations of Medical Sciences forms and reports it to appropriate authorities within 15 days (or 7 in case of threat to the life or death of the patient) from receiving the report, following the data transfer procedure with the applicable law. The SMT will provide an annual patient safety report throughout the clinical trial, including appropriate

information on treatment safety. The Sponsor holds the right to pause or discontinue part of the trial, the entire trial, or the participation of an individual patient.

After trial completion, all the patients will receive further treatment instructions, prescription for ADHD treatment and referral to appropriate health provider facilities. Reference diabetology centres will provide continued diabetes care under NHF.

Dissemination plan

Results will be submitted for publication in leading international scientific journals in diabetes care, endocrinology and psychiatry. Results will also be shared during relevant national and international congresses and conferences. The cooperation between the Sponsor and patient organization (affiliation 13) will be continued after the Trial's completion to increase awareness of the impact of psychiatric diseases in patients with T1D. The study`s results will also be communicated to the funding agency and national healthcare policy makers.

Discussion

Despite the favorable opinion of the Polish Agency for Health Technology Assessment and Tariff System, LDX is still unavailable for Polish patients outside this clinical trial. We will provide data collected during this Trial for consideration of the Agency, to promote discussion about the availability of LDX and advocate for it being widely accessible (if not reimbursed). We will also perform a specific cost-effectiveness analysis for the particular population of children with ADHD and T1D, and investigate possible costs and benefits of considering LDX as a first-line treatment in this group of patients, justified by the system savings provided by possibly-improved diabetes control.

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Author contribution: AM, JC, HKK, WF, AB, KB – written the article, prepared the clinical trial protocol; WF, AB, AM, KB – supervised the clinical trial registration; EK – translated the clinical trial protocol and written the supplementary materials; BM, ASz, ACh, PJCh, MM, IM,

AK, TW, WF, AB – consulted the manuscript and the clinical trial protocol; MZ –supervised patients consultation of the clinical trial. All authors reviewed the results and approved the final version of the manuscript. We comply to the ICMJE guidelines.

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Competing interest statement: Authors have no conflict of interest to declare. In particular, manufacturer`s of neither studied drugs contributed to the study design or provided any support (financial or other) to the Sponsor of the study (Medical University of Lodz). The study is a non-commercial clinical trial funded by the Polish Medical Research Agency.

Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH – methylphenidate. ** - if needed on-demand consultation

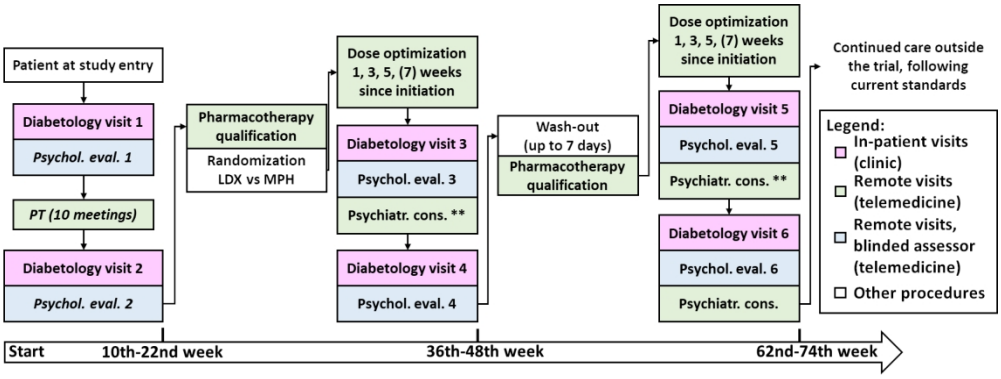

Figure 1. Simplified study design flowchart. PT – parental training, LDX – lisdexamphetamine, MPH – methylphenidate. ** - if needed on-demand consultation

315x117mm (150 x 150 DPI)

Supplementary Table 1. Study schedule. The order of treatment (A/B) will be decided at randomization (allocation step). Names of visits corresponding to Figure 1 are included.

			STUDY PERIOD								
			Enroll	PT	Allocate	Post-allocation					
	DURATION		*1 week*	*10-22 weeks*	*1 week*	*First treatment (6 months)*			*Second treatment (6 months)*		
ENROLLMENT	Eligibility screen		X		X			X			
	Informed consent		X								
	Randomization (to A/B)				X						
INTERVENTION	Parent training in behaviour management			X							
	Cross-over	MPH				A	A	A	B	B	B
		LDX				B	B	B	A	A	A
ASSESSMENTS	Conners 3, PedsQL questionnaires		Psychological evaluatlion 1		Psychological evaluation 2		Psychological evaluation 3	Psychological evaluaton 4		Psychological evaluaton 5	Psychological evaluaton 6
	Diabetes control (HbA1c, CGM)		Diabetological visit 1		Diabetological visit 2		Diabetological visit 3	Diabetological visit 4		Diabetological visit 5	Diabetological visit 6
	Anthropometric, BP, HR measruement										
	Urine tests, ECG with QT segment assessment, ophthalmologic consultation										
	Psychiatric consultation				LDX/MPH qualification	Dose optimization	*Additional dose adjustment		Dose optimization	*Additional dose adjustment	Referral to care under National Health Fund

*optional, up to the Investigator, only lowering of dose allowed

SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	ItemNo	Description	Line
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	**1-4**
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	**S2: 5-8** **S2: 10**
	2b	All items from the World Health Organization Trial Registration Data Set	**S2: 4-150**
Protocol version	3	Date and version identifier	**S2: 3**
Funding	4	Sources and types of financial, material, and other support	**569-570**
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	**5-8** **563-568**
	5b	Name and contact information for the trial sponsor	**S2: 14** **S2: 16-19**
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	**151-156** **229-232** **271-272** **277-281** **570-571** **S2: 152-166**
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the Trial, if applicable (see Item 21a for data monitoring committee)	**S2: 167-201**
Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the Trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	**87-144** **S1: 58-121** **S1: 299-410** **S1: 637-673** **S1: 885-897** **S1: 944-983**
	6b	Explanation for choice of comparators	**323-355**
Objectives	7	Specific objectives or hypotheses	**145-148** **289-322**
Trial design	8	Description of trial design including type of Trial (eg, parallel group, cross-over, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	**151-152** **250-252** **S2: 98-99**
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	**195-215**
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	**167-196**
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	**216-273** **S2: 28-32**
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	**166-194** **253-269** **433-434** **S2: 311-382** **S2: 515-517** **S2: 752-757**
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	**258-263** **441-443** **S2: 142-147**
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the Trial	**424-425**
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline,	**289-355** **S2: 103-142**

		final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and wash-outs), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	**Figure 1** **Table 1** **224-273**
Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	**378-398** **S2: 101**
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	**151-156** **158-164** **196-226** **387-398**
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	**274-281**
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	**274-281**
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	**274-281**
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	**282-288** **S2: 28-32** **S2: 103-142** **S2: 179-182**
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the Trial	**282-288**
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	**289-323** **323-355** **S2: 122-298** **S2: 420-431** **S2: 438-458** **S2: 674-884** **S2: 983-1195**
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	**237-242** **369-374**
Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	**399-403** **S2: 174-150** **S2: 183-188**
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	**356-377**
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	**356-377**
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	**369-374**
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	**S2: 167-201**
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the Trial	**423-434**
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	**425-434**
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	**404-410**
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	**416-418** **S2: 143-144**

Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	**420-422**
Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	**218-225** **S1: 509-537** **S1: 1226-1259**
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	**218-225** **S1: 412-419** **S1: 476-484** **S1: 898-903** **S1: 1214-1221**
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the Trial	**286-288** **334-355** **366-368** **399-403** **424-433** **S1: 491-503** **S1: 538-600** **S1: 892-897** **S1: 1261-1322** **S2: 147-150**
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall Trial and each study site	**571**
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	**405-410** **424-433** **S2: 183-188**
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	**438-443** **S1: 223-225**
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	**437-442** **S1: 51-57** **S1: 380-382** **S1: 470-475** **S1: 1209-1213**
	31b	Authorship eligibility guidelines and any intended use of professional writers	**564-569**
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	**439-443** **S1: 491-503** **S1: 538-600** **S1: 892-897** **S1: 1261-1322**
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	**S1: 30-601** **S1: 616-906** **S1: 922-1322**
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current Trial and for future use in ancillary studies, if applicable	**S1: 412-419** **S1: 476-484** **S1: 898-903** **S1: 1214-1221**

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.