SUPPLEMENTARY MATERIAL

Supplementary Table 1. Schedule of assessments for treatment-naïve participants

	Screening	Wk1	Wk2	Wk3	Wk4	Wk5	Wk13	Wk25	Wk37	Wk49	Wk61 and every 12 weeks thereafter	Wk73 and every 24 weeks thereafter	Wk98 and every 48 weeks thereafter (except Wk289)	Wk145	Wk313/early termination†	Safety F/U visit†
Informed consent	x															
Inclusion/exclusion criteria	x															
Medical history and demographic data	x															
Height	x									x			x	x	x	
Body weight	x	x				x	x	x	x	x	x			x	x	x
Physical examination‡	x	x				x	x	x	x	x	x			x	x	x
Vital signs	x															
Concomitant medications§		x	x	x	x	x	x	x	x	x	x			x	x	x
Electrocardiogram	x															
Haematology/blood chemistry¶	x							x		x		x		x	x	x
FVIII inhibitors‡‡	x		x					x		x		x		x	x	x
Questionnaires on bleeds and drugs used††		←											→	x	x	x
Activities survey		x				x	x	x	x	x	x			x		
Adverse events§§		←											→	x	x	x
MRI joint assessment¶¶		x												x	x	
HJHS joint¶¶ assessment		x						x		x			x	x	x	
Pregnancy test	x															

Permissible time windows: The permissible length of time between screening and enrolment is ≤28 days. Patients who are not enrolled within 28 days after screening must be rescreened. Emicizumab may be injected within a window of 3 days before the scheduled treatment date (scheduled date –3 days). If the participant forgets or is unable to inject emicizumab within the permitted dosing window, the injection should be given as soon as possible within 3 days after the scheduled treatment date in participants receiving QW dosing, within 7 days after the scheduled treatment date in participants receiving Q2W dosing, and within 14 days after the scheduled treatment date in participants receiving Q4W dosing. To monitor treatment compliance when emicizumab is administered at home by the patient or caregiver, the patient/caregiver will be asked about emicizumab usage at each scheduled study visit.

BU, Bethesda unit; eCRF, electronic case report form; FVIII, factor VIII; F/U, follow-up; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Wk, week.

†The early termination visit is conducted when a participant is discontinued from emicizumab after having received emicizumab treatment. The safety follow-up visit is conducted 24 weeks after emicizumab is discontinued. This visit will not be performed for participants who continue emicizumab treatment after the end of the study.

‡A complete physical examination should be performed at screening. Subsequent physical examinations will evaluate joints (bleeds, arthropathy findings) and skin (contusions, haematomas, injection site reactions, lipodystrophy), as well as other organs if clinically necessary and/or new or worsened adverse events are observed.

§Treatment for bleeds requiring treatment with coagulation factors will be entered on the eCRF at the study site based on the information provided in the questionnaires on coagulation factors used.

¶Haematological laboratory tests included haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, differential white blood cell count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), mean cell volume, mean cell haemoglobin concentration, and red cell distribution width. Blood chemistry tests included sodium, potassium, chloride, calcium, phosphorus, magnesium, glucose, blood urea nitrogen, creatinine, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, and uric acid.

††The participant must have a negative result (<0.6 BU/mL) on an FVIII inhibitor assay conducted at screening or within 8 weeks prior to enrolment.

‡‡The bleeds/drugs used logs should be completed by the caregiver. The caregiver will complete the Emicizumab Injection Log each time emicizumab is injected, the Bleeding Episode Log each time a bleed requiring treatment with coagulation factors occurs, and the Coagulation Factors Log each time coagulation factors are used. When

a participant is discontinued from emicizumab treatment, the caregiver will continue to update the Bleeding Episode Log and Coagulation Factors Log until completion of the safety follow-up visit.

§§The participant will inform the investigator about adverse events at each study visit. Adverse events will be reported on the eCRF by the investigator.

¶¶The MRI and HJHS joint assessments will be performed within ±28 days of the scheduled time point at Week 1. The Week 145 and Week 313 MRI joint assessments may be performed within ±84 days of the scheduled time point. The HJHS joint assessment may be performed within ±28 days of the scheduled time point at Weeks 25 and 49 and within ±84 days of the scheduled time point thereafter.

Supplementary Table 2. Schedule of assessments for participants entering from HOHOEMI

	Screening	Wk25†	Wk37	Wk49	Wk61 and every 12 weeks thereafter	Wk73 and every 24 weeks thereafter	Wk97 and every 48 weeks thereafter (except Wk289)	Wk145	Week313/ Early termination‡	Safety F/U visit‡
Informed consent	x									
Inclusion/exclusion criteria	x									
Medical history and demographic data	x									
Height				x			x	x	x	
Body weight		x	x	x	x			x	x	x
Physical examination§		x	x	x	x			x	x	x
Concomitant medications¶		x	x	x	x			x	x	x
Haematology/blood chemistry††		x		x		x		x	x	x
FVIII inhibitors		x		x		x		x	x	x
Questionnaires on bleeds and drugs used‡‡		←	—	—	—	—	→	x	x	x
Activities survey		x	x	x	x			x		
Adverse events§§		←	—	—	—	—	→	x	x	x
MRI joint assessment¶¶								x	x	
HJHS joint assessment¶¶				x			x	x	x	

Emicizumab may be injected within a window of 3 days before the scheduled treatment date. If the participant forgets or is unable to inject emicizumab within the permitted dosing window, the injection should be given as soon as possible within 3 days after the scheduled treatment date in participants receiving QW dosing, within 7 days after the scheduled treatment date in participants receiving Q2W dosing, and within 14 days after the scheduled treatment date in participants receiving Q4W dosing. To monitor

treatment compliance when emicizumab is administered at home by the patient or caregiver, the patient/caregiver will be asked about emicizumab usage at each scheduled study visit.

BU, Bethesda unit; eCRF, electronic case report form; FVIII, factor VIII; F/U, follow-up; HJHS, Hemophilia Joint Health Score; MRI, magnetic resonance imaging; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; Wk, week.

†Day 1 (Wk 1) is defined as the day of administration of the first dose of emicizumab in HOHOEMI. Week numbers of visits are ongoing from HOHOEMI in participants entering from HOHOEMI.

‡The early termination visit is conducted when a participant is discontinued from emicizumab after having received emicizumab treatment. The safety follow-up visit is conducted 24 weeks after emicizumab is discontinued. This visit will not be performed for participants who continue emicizumab treatment after the end of the study.

§Physical examinations will evaluate joints (bleeds, arthropathy findings) and skin (contusions, haematomas, injection site reactions, lipodystrophy), as well as other organs if clinically necessary and/or new or worsened adverse events are observed.

¶Treatment for bleeds requiring treatment with coagulation factors will be entered on the eCRF at the study site based on the information provided in the questionnaires on factors used.

††Haematological laboratory tests included haemoglobin, haematocrit, platelet count, red blood cell count, white blood cell count, differential white blood cell count (neutrophils, eosinophils, lymphocytes, monocytes, basophils), mean cell volume, mean cell haemoglobin concentration, and red cell distribution width. Blood chemistry tests included sodium, potassium, chloride, calcium, phosphorus, magnesium, glucose, blood urea nitrogen, creatinine, total bilirubin, total protein, albumin, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase, creatine phosphokinase, and uric acid.

‡‡The bleeds/drugs used logs should be completed by the caregiver. The caregiver will complete the Emicizumab Injection Log each time emicizumab is injected, the Bleeding Episode Log each time a bleed requiring treatment with coagulation factors occurs, and the Coagulation Factors Log each time coagulation factors are used. When a participant is discontinued from emicizumab treatment, the caregiver will continue to update the Bleeding Episode Log and Coagulation Factors Log until completion of the safety follow-up visit.

§§The participant will inform the investigator about adverse events at each study visit. Adverse events will be reported on the eCRF by the investigator.

¶¶MRI and HJHS joint assessments will be performed within –84 to 0 days of the scheduled time point. If an assessment cannot be performed within –84 to 0 days of the scheduled time point, the assessment may be performed up to 84 days after the scheduled time point.

Supplementary Table 3. Adverse event severity grading scale for events excluded from World Health Organization toxicity grading scale

Grade	Severity
1	**Mild**: Transient or mild discomfort (<48 hours); no medical intervention or therapy required
2	**Moderate**: Mild to moderate limitation in activity; some assistance may be needed; no or minimal medical intervention or therapy required
3	**Severe**[†]: Marked limitation in activity; some assistance usually required; medical intervention or therapy required; hospitalization possible
4	**Life-threatening**: Extreme limitation in activity; significant assistance required; significant medical intervention or therapy required; hospitalization or hospice care possible

Developed by the Division of Microbiology and Infectious Diseases.

[†]Regardless of severity, some events may also meet seriousness criteria; the terms “serious” and “severe” are not synonymous, both need to be independently assessed.

Supplementary Table 4. Seriousness criteria of adverse events

Number	Criteria
1	Is fatal (i.e., the adverse event causes or leads to death)
2	Is life threatening† (i.e., the adverse event, in the view of the investigator, places the participant at immediate risk of death)
3	Requires or prolongs inpatient hospitalization
4	Results in persistent or significant disability/incapacity (i.e., the adverse event results in substantial disruption of the participant's ability to conduct normal life functions)
5	Is any serious adverse event associated with the pregnancy of a female participant (e.g., an event in the foetus, an event in the mother during or after pregnancy, or a congenital anomaly/birth defect in the child)
6	Is a significant medical event in the investigator's judgment (e.g., may jeopardize the participant or may require medical/surgical intervention to prevent one of the outcomes listed above)

†This does not include any adverse event that, had it occurred in a more severe form or could continue, might have caused death. The terms "severe" and "serious" are not synonymous; severity refers to the intensity of an adverse event.

Supplementary Table 5. Baseline characteristics of participants enrolled in AOZORA

	Participants entering from HOHOEMI N = 10	New participants N = 20	Total participants N = 30
Age (years), median (range)	5.8 (1.5–10.7)	3.7 (0.7–11.0)	4.1 (0.7–11.0)
Age category, n (%)			
0 to <2 years	2 (20.0)	4 (20.0)	6 (20.0)
2 to <6 years	3 (30.0)	9 (45.0)	12 (40.0)
6 to <12 years	5 (50.0)	7 (35.0)	12 (40.0)
Male, n (%)	10 (100)	20 (100)	30 (100)
Weight (kg), median (range)	19.4 (9.5–35.6)	15.9 (7.3–63.1)	16.3 (7.3–63.1)
Treatment regimen with coagulation factor products prior to enrolment, n (%)			
Episodic FVIII	0 (0)	2 (10.0)	2 (6.7)
Prophylactic FVIII	10 (100)	17 (85.0)	27 (90.0)
Previously untreated participants	0 (0)	1 (5.0)	1 (3.3)
Participants previously treated with ITI therapy, n (%)	2 (20.0)	3 (15.0)	5 (16.7)
Duration of ITI (years), median (range)	0.8 (0.4–1.1)	2.3 (0.6–5.3)	1.1 (0.4–5.3)
Period from end of ITI to emicizumab initiation (years), median (range)	3.9 (0.3–7.4)	3.2 (1.1–5.0)	3.2 (0.3–7.4)
Participants with target joints, n (%)	1 (10.0)	0 (0)	1 (3.3)

FVIII, factor VIII; ITI, immune tolerance induction.

Supplementary Table 6. Baseline participant IPSG MRI Scale; the number of joints with a positive score (≥1 point) according to each item

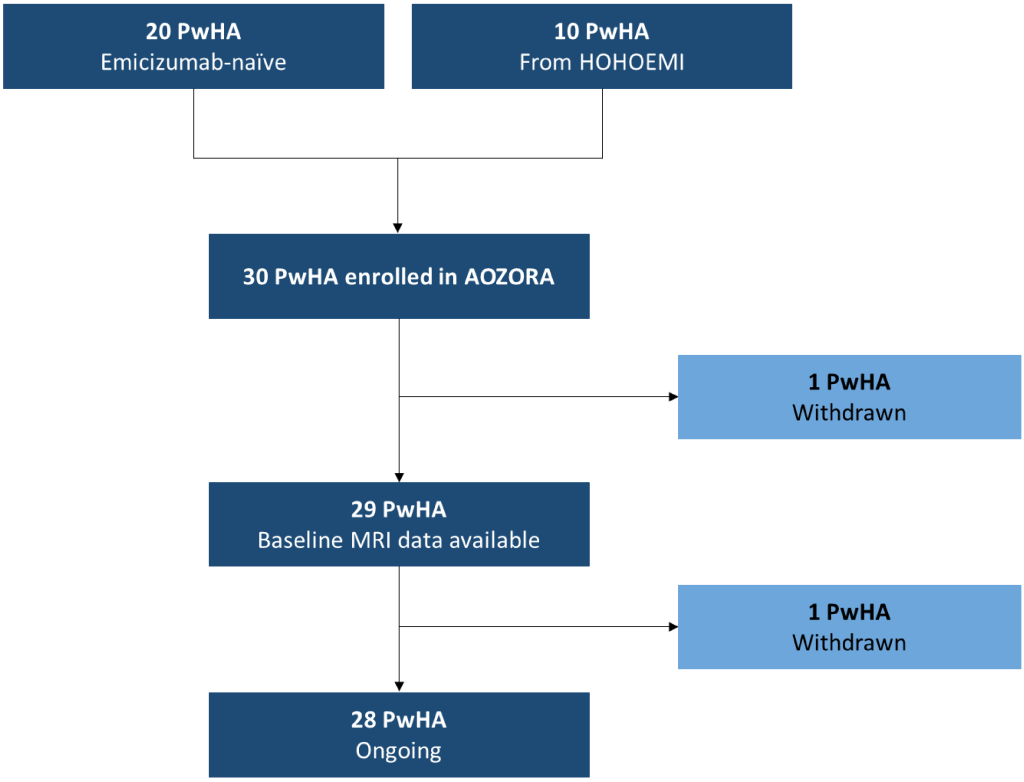
	Knee (N = 58)	Ankle (N = 58)	Total (N = 116)
Soft tissue changes, n (%)†	12 (20.7)	16 (27.6)	28 (24.1)
Effusion/haemarthrosis, n (%)	11 (19.0)	10 (17.2)	21 (18.1)
Small, n (%)	11 (19.0)	10 (17.2)	21 (18.1)
Moderate, n (%)	0	0	0
Large, n (%)	0	0	0
Synovial hypertrophy, n (%)	1 (1.7)	9 (15.5)	10 (8.6)
Small, n (%)	1 (1.7)	7 (12.1)	8 (6.9)
Moderate, n (%)	0	2 (3.4)	2 (1.7)
Large, n (%)	0	0	0
Haemosiderin, n (%)	1 (1.7)	9 (15.5)	10 (8.6)
Small, n (%)	1 (1.7)	7 (12.1)	8 (6.9)
Moderate, n (%)	0	2 (3.4)	2 (1.7)
Large, n (%)	0	0	0
Osteochondral changes, n (%)	0	1 (1.7)	1 (0.9)
Surface erosions involving subchondral cortex or joint margins, n (%)	0	1 (1.7)	1 (0.9)
Subchondral cysts, n (%)	0	0	0
Cartilage degradation, n (%)	0	0	0

IPSG, International Prophylaxis Study Group; n, number of joints; MRI, magnetic resonance imaging.

†Effusion/haemarthrosis, synovial hypertrophy and haemosiderin may be scored more than once in the same joint.

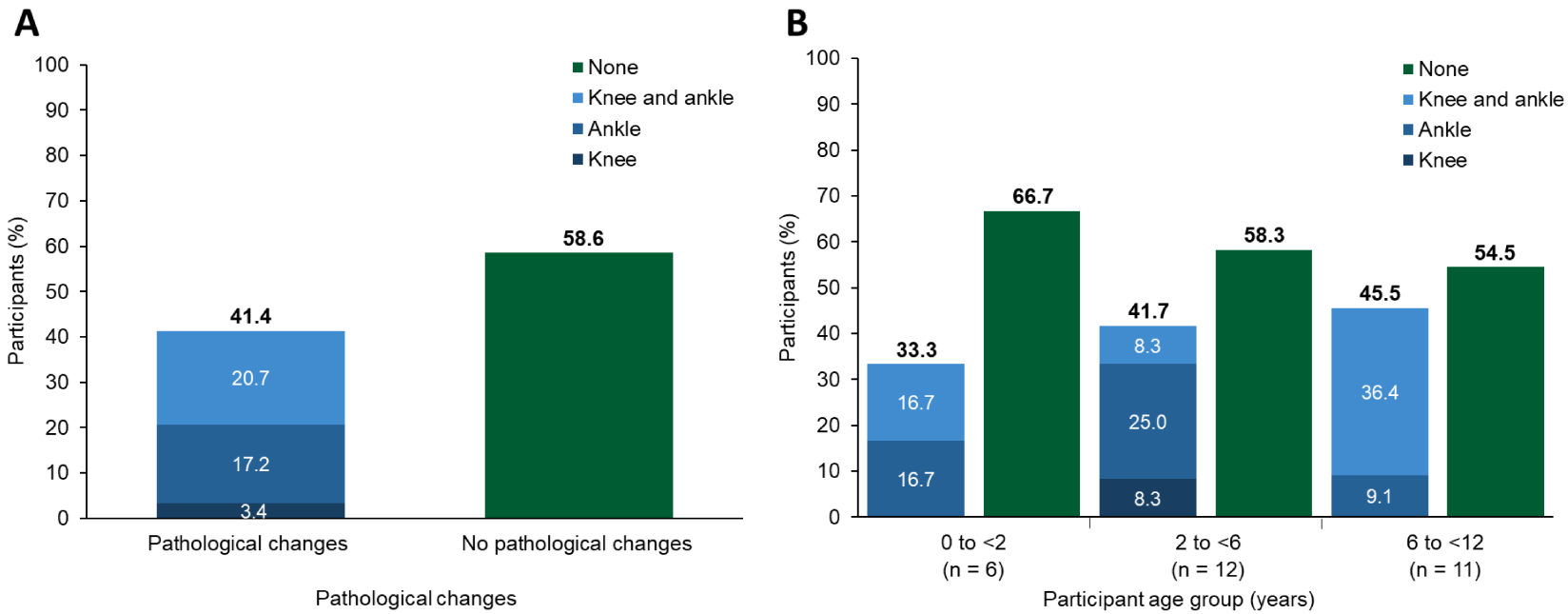
Bilateral ankles and knees were centrally scored using the additive MRI scale of the IPSG.

Supplementary Figure 1. Participant disposition



MRI, magnetic resonance imaging; PwHA, persons with haemophilia A

Supplementary Figure 2. Participants with pathological changes in the knee and ankle joints at baseline



A) Proportions of participants with and without pathological changes at baseline. **B**) Proportions of participants in different age groups with pathological changes in joints at baseline.

Participants with a positive score (>1) of the additive IPSG MRI scale on at least one joint are defined as having pathological change (soft tissues changes and osteochondral changes). MRI evaluation was performed on 29 participants.

IPSG, International Prophylaxis Study Group; MRI, magnetic resonance imaging

Activities questionnaire

After carefully reading the following instructions, enter the activities of your child during the week.

Instructions

(1) Use a ballpoint pen, felt-tip pen, or other writing utensil with permanent ink.
(2) Submit the completed questionnaire to the physician or study collaborator at the next study visit.
(3) If you make a mistake, do not use the correction fluid. Revise the text so that the changes are apparent, by, for example, drawing a strikethrough line through the mistaken text.
(4) If you misplace the questionnaire, contact the study site.

Patient No.:

Period covered: 20 / / ～ 20 / / (Wk)

■ Record the duration of activities in the following week, using the Table of Activity Categories provided below as reference.

- For activities performed for at least 15 minutes in one day, select the type of activity from the Table of Activity Categories provided below and record the appropriate category number and the duration of the activity. (If you have trouble determining which category is appropriate, select the category with the highest number.). If you have more than one activity in the same category during a day, enter the total time.
- If activities belonging to different categories are performed in the same day, enter the additional activities in the Activities 2, 3, and 4 columns. If an activity causes bleeding, check the box in the "activity-related bleeding" field and enter the number of bleeds in the parentheses. If you have more than one site of bleeding, count each as one time (e.g., If you have bleeding in two sites after falling, please enter "2").

	Item	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:
Activity 1	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 2	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 3	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 4	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 5	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))

	Item	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:	M: D: 20:
Activity 6	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity7	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 8	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 9	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))
Activity 10	Category No.							
	Activity duration	min	min	min	min	min	min	min
	Activity-related bleeds	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))	□ (bleed(s))

Physician Signature:_____ Confirmation date:_____

■ Table of Activity Categories

Category	Activity type	Examples
1	Home duties	Vacuuming, cleaning, dusting (e.g., with mop), sweeping, cooking, painting, gardening, lawn mowing, shopping, picking up rubbish
2	Jogging/walking/sprinting	Transport, recreation, jogging, sprint races, long distance running, marching, athletics, hiking, cross country running
3	Swimming	Freestyle, breaststroke, butterfly, backstroke, kickboard, treading water
4	Light play	Playing with friends, playing with dog, playing with blocks, drumming, Wii fit or Wii sports, jumping, slide, see-saw, frisbee, skipping, hula hoop, swing, card games, theme parks
5	Non-contact sports	Archery, darts, bowling, golf, fishing, tai chi, pool, table tennis, marbles, badminton
6	Dancing	Hip hop, jazz, ballroom dancing, contemporary dance, folk dancing
7	Light gym activities	Lifting weights, exercise using gym equipment, cardio, stretching, physiotherapy, gym class exercises
8	PE	School PE lessons
9	Low-contact ball games	Handball, playing catch
10	Throwing	Shot put, javelin, discus
11	Water play	Wind surfing, snorkeling, scuba diving, rowing, canoeing, lifesaving
12	Water activities	Surfing, waterskiing, diving, water slides, rafting, sailing
13	Unstructured park/open space activities	Jumping castle, trampolining, climbing, tug-o-war, climbing trees, swinging from ropes, playing on play equipment
14	Gymnastics	Artistic, rhythmic, acrobatics, competitive trampolining
15	Low-risk riding activities	Bike riding, riding scooter, riding horse, rollerblading, roller-skating
16	Wilderness	Rock climbing, abseiling, chopping wood

Category	Activity type	Examples
17	Hard ball games/training	Baseball, softball, cricket
18	Running games/jumping	Chasings, running long jump, running high jump, hurdles
19	Racquet sports	Tennis, squash
20	Low-contact sports	Soccer, basketball, volleyball, field hockey, football umpire, school sport (club activities)
21	Winter sports	Skiing, ice-skating, sledding, snowboarding
22	Martial arts	Karate, Kung Fu, Tae Kwon Do, Judo, boxercise, boxing drill
23	Contact/collision sports	Rugby, American football, ice hockey, wrestling, boxing
24	Motor sports	Motocross
25	High-risk riding activities	Skateboarding, rip-stick
26	Rough play	Wrestling, dodge ball