

ONLINE DATA SUPPLEMENT

Supplementary Appendix 1. Composition and some characteristics of proprietary marketed nebulized inhaled corticosteroids*

Drug	BUD	FLU	BDP	FP
Strength	0.125, 0.25 and 0.5 mg/ml	0.5 and 1 mg/ml	0.4 mg/ml	0.5 and 1 mg/ml
Non drug composition	Disodium edetate, polysorbate 80, citric acid monohydrate, trisodium citrate dihydrate, sodium chloride, and water for injection	Propylene glycol, sodium chloride, citric acid monohydrate, trisodium citrate dihydrate and water for injection	Polysorbate 20, sorbitan laureate, sodium chloride, and water for injection.	Polysorbate 20, sorbitan laureate, sodium phosphate dihydrate, dibasic sodium phosphate, sodium chloride and water for injection
Osmolarity, mOsmol/Kg	280	NA	300	290
pH	4.4	NA	4.5-5.0	6.0
Dynamic viscosity, mPas	1.1	NA	1.8	0.97
Surface tension, mN/m	30-50	NA	55-60	53.8
Water solubility mcg/ml	20	140	NA	0.14
Mean diameter of micronized particles, μm	2.4-3.0	NA	3.7	NA

Legend: BUD = nebulized budesonide; BDP = nebulized beclomethasone dipropionate; FP = nebulized fluticasone propionate; FLU = febulized flunisolide; NA =not available

*From reference 33-35 and the following links:

http://www.pharmcast.com/Patents100/Yr2005/Nov2005/112205/6967017_Steroid112205.htm

<http://www.docstoc.com/docs/51553882/Fluticasone-Propionate-Nebulizable-Formulations---Patent-5993781#viewer-area>

http://www.surechem.org/index.php?Action=document&docId=1009463&db=EPA&tab=desc&lang=&db_query=0%3A%3A0%3A%3A0%3A&markupType=all

ONLINE DATA SUPPLEMENT

Supplementary appendix 2. *In vitro* studies evaluating aerosol properties of nebulized budesonide

Nebulizer system	Total drug dosage in mg	Fill volume in ml	MMAD in μm	GSD in μm	Respirable fraction in % of inhaled mass	Inhaled Mass, mean % of label charge	Reference number
SideStream/ 8 lpm	1	4	3.6 ^d	1.7	75	35 ¹	36
AeroTechII/ 10 lpm	1	4	2.4 ^d	1.6	92	18 ¹	36
AeroTechII/ 6 lpm	1	4	2.3 ^d	1.4	98	6 ¹	36
Aerosonic ultrasonic	1	4	2.9 ^d	1.4	92	9 ¹	36
LL/ Boy 37	1	2				23 ⁶	45
LL/ Boy 38G	1	2				20 ⁶	45
LC Plus/ Boy 38G	1	2				23 ⁶	45
LC Plus/ WalkBoy	1	2				20 ⁶	45
Cirrus/ Novair II	0.5	2				21 ² /7 ⁴ /7 ¹¹ /1 ¹²	46
Sidestream/ PortaNeb 50	0.5	2				30 ² /4 ⁴ /4 ¹¹ /1 ¹²	46
LC Plus/ ProNebTurbo	0.5	2				35 ² /16 ⁴ /15 ¹¹ /5 ¹²	46
LC Plus/ Master	1	2	5.0 ^c	2.1		16.6 ¹⁰	47
LC Plus/ PulmoAide	1	2	5.2 ^c	2.3		17.8 ¹⁰	47
Inspiron/ PulmoAide	1	2	4.7 ^c	2.1		14.8 ¹⁰	47
MistyNeb/ PulmoAide	1	2	5.5 ^c	2.3		14.6 ¹⁰	47
Aiolos/ CR60	1	2	4.3 ^c	2.1		13.4 ¹⁰	47
UpDraft II/ Hudson	1	2	3.8 ^c	2.2		14.2 ¹⁰	47
UpDraft II/ MediMist	1	2				14.5 ¹⁰	47
UpDraft II/ PulmoAide	1	2	4.3 ^c	2.9		14.6 ¹⁰	47
DeVilbiss ultrasonic	1	2				4.0 ¹⁰	47
DeVilbiss 646/ PulmoAide	1	2				7.6 ¹⁰	47
DeVilbiss 644/ PulmoAide	1	2				7.5 ¹⁰	47
AeroTechT/ Schuko	1	2				9.0 ¹⁰	47
AeroTechY/ Schuko	1	2				7.5 ¹⁰	47
PARI 1460 DuraNeb 2000	1	2				9.9 ¹⁰	47
PulmoNeb/ PulmoAide	1	2	4.2 ^c	2.0		9.6 ¹⁰	47
PulmoNeb/ PulmoAide Traveller	1	2	4.0 ^c	2.1		11.8 ¹⁰	47
AvaNeb/ Hudson	1	2	3.8 ^c	2.0		12.7 ¹⁰	47
AvaNeb/ MediMist	1	2				13.5 ¹⁰	47
AvaNeb/ PulmoAide	1	2	4.2 ^c	2.0		13.8 ¹⁰	47
IsoNeb A/ Hudson	1	2				2.6 ¹⁰	47
IsoNeb B/ Hudson	1	2				1.6 ¹⁰	47
IsoNeb A/ MediMist	1	2				4.2 ¹⁰	47
LC Plus/ ProNeb Turbo	0.5	2	4.1 ^b	2.1	70	22 ³ /18 ¹¹	48
LC Star/ ProNeb Turbo	0.5	2	3.8 ^b	1.9	77	18 ³ /13 ¹¹	48
VentStream/ PortaNeb 50	0.5	2	3.1 ^b	2.0	87	10 ³ /6.5 ¹¹	48
LC Star/ProNeb Ultra	1	2	5.1 ^h	2.0	85	28 ⁵	49
eFlow	1	2	3.9 ^h	2.3	83	30 ⁵	49
LC Plus/ NA	0.5	2				15 ¹⁰	51
Aerodose	0.083	0.3				58 ¹⁰	51
LC Plus/ ProNeb Ultra	1	2	5.0 ^d	4.0	63	25 ⁵	33
Multisonic ultrasonic	1	2	3.8 ^d	3.4	75	5 ⁵	33
eFlow Baby	1	2	3.6 ^d	3.0	92	25 ⁵	33
NEU22	1	2				7-29 ⁵	53
Aerodose 5.7	1	2	2.4 ⁿ	2.2	82		54
LC Star/O2 8 lpm	1	2	3.5 ⁿ	1.0	69		54
Aeroneb Go	0.5	2	3.1 ^d	1.6		22 ⁶	55
LC Plus/ NA	0.5	2	3.8 ^d	2.3		18 ⁶	55
LC Plus/ ProNeb Ultra	0.5	2	5.3 ¹	2.1	47	25 ⁵ /12.5 ¹¹ /9 ¹⁵	56
eFlowBaby	0.5	2	3.2 ¹	1.6	83	25 ¹⁵	56
BimboNeb	0.5	2	4.5 ⁸	2.3	58-66	14 ³ /10 ¹¹	57
Nebula	0.5	2	3.4 ⁸	2.2	73-82	8 ³ /9 ¹¹	57

ONLINE DATA SUPPLEMENT

Updraft II/ PulmoAide/ FM	0.25	2				19 ¹⁷ /4 ¹⁸	58
Updraft II/ PulmoAide/ sealed FM	0.25	2				46 ¹ /24 ¹⁷ /10 ¹⁸	58
LC Plus/ Master/ Fish FM	0.25	2				12 ¹⁷ /9 ¹⁸	58
LC Plus/ Master/ sealed	0.25	2				46 ¹ /19 ¹⁷ /10 ¹⁸	58
Cirrus/ Master	1	2	3.3 ^f		71	12 ⁵	59
LC Plus/ Master	1	2	4.5 ^f		51	27 ⁵	59
Comp Air Elite	1	2	7.4 ^f		8	29 ⁵	59
LC Plus/ 7 lpm	0.25		5.2-5.6 ⁿ	2.0	21-15		60
VixOne/7 lpm	0.25		3.0-5.3 ⁿ	1.9	20-12		60
Sidestream/PortaNeb	1	2	ⁿ		56		37
PARI LC Plus/PronebUltra II	0.5	2	4.9 ^a	1.7	51	37 ²	61
PARI LC Plus/Proneb Ultra II	0.5	4	4.6 ^a	1.8	56	46 ²	61
PARILCPlus/ProNebUltraII	0.5	2	7.4 ⁱ	2.1	23		62-63
PARILCPlus/ProNebUltraII ^o	0.5	2	6.8 ⁱ	2.1	29		62-63
MicroPlus/MicroElite	0.5	2	5.3 ^e		45	10 ⁶ /7 ¹⁹	65
LC Sprint/Trek S	0.5	2	5.0 ^e		47	10 ⁶ /7 ¹⁹	65
LC Plus/Proneb Ultra/ LaerdalFM	0.5	2	7.8 ^m			14 ¹⁶	64
LC Plus/Proneb Ultra/ FishFM	0.5	2	7.6 ^m			13 ¹⁶	64
MistyNeb/Proneb Ultra /SalterFM	0.5	2	9.0 ^m			3 ¹⁶	64
MistyNeb/Proneb Ultra /Fish mask	0.5	2	7.3 ^m			8 ¹⁶	64
Sidestream/PortaNeb	2	4	7.1 ^l	1.8	30	27 ⁵	38
NEU22	0.5	1	6.4 ^l	1.7	41	35 ⁵	38
AeroEclipseII/ PortaNeb	0.5	2	5.7 ^e	1.8		20 ¹⁴	68
Assister KN-180	0.5	2	7.8 ^e	1.9		5 ¹³ /11 ¹⁴	68
Genki	0.5	2	7.3 ^e	1.8		4 ¹³ /11 ¹³	68
Hudson/ PulmoAide 3655	0.5	2	6.1 ^e	1.7		3 ¹³ /5 ¹⁴	68
Comp Air Elite	0.5	2	7.0 ^e	1.9		8 ¹³ /18 ¹⁴	68
Medel SkyNeb	0.5	2	6.8 ^e	1.9		8 ¹³ /16 ¹⁴	68
Mefar2000/ Voyage	0.5	2	7.7 ^e	1.8		6 ¹³ /12 ¹⁴	68
Mefar2000/ Promenade-car	0.5	2	7.5 ^e	1.7		5 ¹³ /10 ¹⁴	68
Mefar2000/ EuroSol	0.5	2	7.8 ^e	1.8		5 ¹³ /9 ¹⁴	68
MicroMist/ PulmoAide 5650N	0.5	2	6.5 ^e	1.8		3 ¹³ /11 ¹⁴	68
Millicon S	0.5	2	7.4 ^e	1.8		7 ¹³ /15 ¹⁴	68
Nesco Jet AZ 11	0.5	2	7.7 ^e	1.9		4 ¹³ /10 ¹⁴	68
Nissho	0.5	2	9.9 ^e	2.1		9 ¹³ /15 ¹⁴	68
NE-C13	0.5	2	6.8 ^e	1.8		4 ¹³ /10 ¹³	68
NE-C16	0.5	2	6.9 ^e	1.8		7 ¹³ /10 ¹⁴	68
NE-C28	0.5	2	5.5 ^e	1.7		3 ¹³ /8 ¹⁴	68
NE-C30	0.5	2	5.9 ^e	1.7		3 ¹³ /9 ¹⁴	68
LC Plus/ ProNeb Turbo	0.5	2	6.2 ^e	1.8		9 ¹³ /20 ¹⁴	68
LC Plus/ UniLight	0.5	2	7.2 ^e	1.8		7 ¹³ /14 ¹⁴	68
LC Plus Junior/ ProNeb Turbo	0.5	2	7.6 ^e	1.8		9 ¹³ /18 ¹⁴	68
LC Sprint/ ProNeb Ultra II	0.5	2	5.8 ^e	1.8		4 ¹³ /12 ¹⁴	68
LC Sprint/ Boy Mobile S	0.5	2	6.1 ^e	1.9		6 ¹³ /14 ¹⁴	68
LC Sprint/ ProNeb Turbo	0.5	2	6.6 ^e	1.8		14 ¹⁴	68
LC Sprint Baby/ ProNeb Ultra	0.5	2	4.8 ^e	1.7		4 ¹³ /9 ¹⁴	68
LC Sprint Junior/ ProNeb Ultra	0.5	2	5.9 ^e	1.8		6 ¹³ /13 ¹⁴	68
LC Star/ Master	0.5	2	4.8 ^e	1.8		4 ¹³ /11 ¹⁴	68
LL/ ProNeb Turbo	0.5	2	5.8 ^e	1.8		5 ¹³ /15 ¹⁴	68
SideStream/ VigorMist	0.5	2	5.3 ^e	1.7		1 ¹³ / 4 ¹⁴	68
SideStreamPlus/ MiniElite	0.5	2	7.7 ^e	1.8		5 ¹³ /17 ¹⁴	68
VentStream/ PortaNeb	0.5	2	5.0 ^e	1.7		8 ¹⁴	68
Sidestream/ Inspiron Elite	0.5	2	3.7 ^e		59		67
Sidestream/ Inspiron Elite	0.25	2	3.9 ^e		58		67
Sidestream/ Stratos Pro	0.5	2	4.4 ^e		58		67
Sidestream/ Stratos Pro	0.25	2	4.5 ^e		71		67
Ventstream/ Elite	0.5	2	5.0 ^e		46		67
Ventstream/ Elite	0.25	2	4.5 ^e		51		67
Ventstream/ Stratos Pro	0.5	2	5.1 ^e		44		67

ONLINE DATA SUPPLEMENT

Ventstream/ Stratos Pro	0.25	2	4.5 ^e		50		67
Ventstream/ Stratos Portable	0.5	2	3.3 ^e		69		67
Ventstream/ Stratos Portable	0.25	2	3.5 ^e		66		67
DeVilbiss 800D/ 3655D	0.5	2	4.4 ^e		52		67
DeVilbiss 800D/ 3655D	0.25	2	4.5 ^e		50		67
DeVilbiss 800D/ TravelAire	0.5	2	3.3 ^e		68		67
DeVilbiss 800D/ TravelAire	0.25	2	2.9 ^e		74		67
DeVilbiss 800D/ Comp Air XL	0.5	2	4.2 ^e		55		67
DeVilbiss 800D/ Comp Air XL	0.25	2	3.6 ^e		62		67
LC Plus/ ProNeb Ultra II	0.5	2	7.4 ^c		32	23 ²⁰	67
LC Plus/ ProNeb Ultra II	0.25	2	6.4 ^c		32		67
AeroNeb Go	0.5	1	5.1 ¹				67
AeroNeb Go	0.25	1	4.9 ¹				67
Sidestream/ PortaNeb	1	4	8.3 ¹		23	27 ⁵	39
NEU22	0.25	1	6.2 ¹		38	34 ⁵	39
SideStream/ AirClinic	0.5	4.5	4.2 ¹	1.8	62	37 ¹	69
VentStream/ AirClinic	0.5	4.5	4.9 ¹	1.9	52	20 ¹	69
SideStream/ AirClinic ^o	0.5	4.5	5.0 ¹	3.0	50	19 ¹	69
VentStream/ AirClinic ^o	0.5	4.5	4.3 ¹	1.9	61	18 ¹	69

Legend: ^othe experiments were performed mixing ICSs to the bronchodilators; ^o=generic formulation of nebulized Budesonide; FM = FacemaskTV = Tidal Volume; Ti/Ttot = Duty cycle; lpm =liters per minute; bpm = breaths per minute. Breathing pattern: ¹continuous aspiration at a flow of 15 lpm; ²continuous flow at 28.3 lpm; ³TV 600 ml, 12 bpm, Ti/Ttot 40%; ⁴TV 600 ml, 16 bpm, Ti/Ttot 40%; ⁵TV 500 ml, 15 bpm, Ti/Ttot 50%; ⁶TV 440 ml, 19 bpm, Ti/Ttot 37%; ⁹TV 100 ml, 30 bpm, Ti/Ttot 42%; ¹⁰TV 200 ml, 25 bpm, Ti/Ttot 50%; ¹¹TV 150 ml, 20 bpm, Ti/Ttot 40%; ¹²TV 50 ml, 30 bpm, Ti/Ttot 40%; ¹³50 ml, 30 bpm, Ti/Ttot 33%; ¹⁴TV 155 ml, 25 bpm, Ti/Ttot 50%; ¹⁵Sophia Anatomical Infant Nose Throat (SAINT) TV 100 ml, 30 bpm, Ti/Ttot 42%; ¹⁶TV 50 ml, 25 bpm, Ti/Ttot 40%; ¹⁷207 ml, 37 bpm, Ti/Ttot 41%; ¹⁸TV 75 ml, 20 bpm, Ti/Ttot 40%; ⁶adult breathing pattern; ¹⁹pediatric breathing pattern; ²⁰TV 300 ml, 35 bpm, Ti/Ttot 50. Droplet size distribution: ⁸-stage Westech ACI at a flow of 28.3 lpm; ^oRespirable fraction expressed as percentage of drug leaving nebulizer in particles respectively <5.0 μm; ⁴-stage MSLI impactor at 30 lpm; %RF <6.1 μm; ⁶-stage Marple Personal CI SE 296 at 2 lpm; ⁸-stage ACI Mark II at 28.3 lpm; %RF <5.8 μm; ^oNGI chilled at 15 lpm; %RF <4.7 μm; ⁸-stage ACI impactor at 15 lpm; %RF < 5.0 μm; ⁸-stage MSLI impactor; %RF <4.3 μm/6.8 μm; ⁸-stage Marple 298 at 2 lpm; %RF < 6 μm; ¹NGI at 15 lpm; %RF <5 μm; ⁸-stage Marple 298 at 15 lpm; %RF < 5 μm; ⁷-stage Marple at 2 lpm ; %RF <4.7 μm; ⁸-stage ACI at 28.3 lpm; %RF <4.7 μm

ONLINE DATA SUPPLEMENT

Supplementary appendix 3. *In vitro* studies evaluating aerosol properties of nebulized flunisolide and beclomethasone dipropionate

Nebulizer system	Drug	Total drug dosage in mg	Fill volume in ml	MMAD in μm	GDS in μm	Respirable fraction in % of inhaled mass	Inhaled Mass, mean % of label charge	Reference number
BimboNeb	BDP	0.8	2	6.4 ^a	1.8	28	9 ² /8 ¹¹	50
Nebula	BDP	0.8	2	5.4 ^a	1.9	39	6 ² /8 ¹¹	50
BimboNeb	FLU	0.6	2.6	3.9 ^a	1.8	60	15 ² /9 ¹¹	52
Nebula	FLU	0.6	2.6	3.9 ^a	1.9	60	11 ² /9 ¹¹	52
Cirrus/Master	BDP	0.8	2	4.8 ^b	NA	54	10 ³	59
PARI LC Plus/Master	BDP	0.8	2	7.5 ^b	NA	23	27 ³	59
Comp Air Elite	BDP	0.8	2	10.0 ^b	NA	26	37 ³	59
BimboNeb ^o	BDP	0.8	3	6.3 ^a	1.8	29	23 ² /16.5 ¹¹	66
BimboNeb ^o	FLU	0.6	3	3.7 ^a	2.3	52	20.5 ² /17 ¹¹	66
Nebula ^o	BDP	0.8	3	5.3 ^a	2.0	39	14 ² /15 ¹¹	66
Nebula ^o	FLU	0.6	3	3.7 ^a	2.3	50	11 ² /12 ¹¹	66
SideStream/AirClinic	BDP	0.8	4.5	4.8 ^b	1.7	53	45.5 ¹	69
VentStream/AirClinic	BDP	0.8	4.5	5.0 ^b	1.8	51	34 ¹	69
SideStream/AirClinic ^o	BDP	0.8	4.5	6.2 ^b	1.7	35	37 ¹	69
VentStream/AirClinic ^o	BDP	0.8	4.5	5.5 ^b	1.7	43	39 ¹	69

Legend: ^othe experiments were performed mixing ICS to the bronchodilators. FLU = flunisolide; BDP = beclomethasone dipropionate; TV = Tidal Volume; Ti/Ttot = Duty cycle; bpm = breaths per minute. Breathing pattern imposed to aerosol: ¹continuous aspiration at a flow of 15 lpm; ²TV 600 ml, 12 bpm, Ti/Ttot 40%; ³TV 500 ml, 15 bpm, Ti/Ttot 50%; ¹¹TV 150 ml, 20 bpm, Ti/Ttot 40%; Method evaluating droplet size distribution: ^a4-stage MSLI impactor; % Respirable Fraction <4.3 μm ; ^b8-stage ACI impactor at 15 lpm; % Respirable Fraction < 5.0 μm ; NA = Not available

ONLINE DATA SUPPLEMENT

Supplementary appendix 4. Ex vivo studies of nebulized budesonide in subjects of different ages

Nebulizer system	Subjects, No	Mean age (range) in years	Total drug dose [^]	Inhaled Mass, mean ^o percentage of label claim	Reference number
Acorn22 Mizer/CR60 ^a	6	(0.3-2.5)	0.5	14	80
Spira/7.5 lpm ^{2,5a}	323	(0.5-7)	0.5	11.4-14.8	81
Spira /7.5 lpm ^{1,5a}	323	(0.5-7)	0.5	10.4-15.2	81
Spira/7.5 lpm ^{2,3a}	323	(5-15)	0.5	8.9-12.7	81
Spira /7.5 lpm ^{1,3a}	323	(5-15)	0.5	19.8-21.5	81
Spira/7.5 lpm ^{2,4a}	323	(5-15)	0.5	5.6-6.9	81
Aiolos ¹	52	(0.5-3.3)	0.25	21	82
Aiolos ¹	50	(0.5-3.3)	1	24	82
PARI LL	38	1.5 (0.5-3.3)	1	26	83
Aiolos	38	1.5 (0.5-3.3)	1	13	83
PARI LC Plus/Master ³	12	5 (3-6)	1	25	84
Spira ^{1a}	164	(0.5-7.9)	1	11.4-14.9	85
Spira ^{2a}	163	(0.5-7.9)	1	10.5-14.9	85
Spira ¹	10	(16-52)	0.5	31 ^b	76
Spira ultrasonico ¹	10	(16-52)	0.5	10 ^b	76
Spira ²	11	4 (2.5-5.8)	0.5	18.7	86
Spira ¹	11	4 (2.5-5.8)	0.5	24.0-28.5	86
Spira ²	11	32 (13-52)	1	17	86
Spira ¹	11	32 (13-52)	1	31-33	86
Spira ³	158	(5.1-15.7)	1	17-22	87
Spira ⁴	158	(5.1-15.7)	1	5-7	87
Spira ⁵	158	(5.1-15.7)	1	9-12	87

^ounless otherwise specified; [^] the fill volume was always 2 ml; ^aThe time of nebulization was a fixed period of 5 minutes; ^b the result is available as median mass; ¹breath-synchronized nebulization; ²continuous nebulization; ³mouthpiece; ⁴ loosely fitting face mask; ⁵ tight sealing facemask

ONLINE DATA SUPPLEMENT

Supplementary appendix 5. Characteristics of randomized placebo-controlled blind studies with nebulized ICSS in acute asthma or COPD exacerbations*

Nebulizer setting	Population, number	Mean age (range) in years	Diagnosis	Drug	Drug dosage in mg	Results*	Evaluation times	Reference number
Hudson/ 8 lpm ¹	123	0.75 (0.1-1.5)	Asthma	BUD	0,5 every 4 hrs	↑HLS; HR, DO, SS: NS	Every 24 hrs up to 5 days	173
No details ²	30	(6-18)	Mild-to-moderate asthma	BUD	1 every 20 min up to 3 doses	↑HLS (at 48 hrs); ↑SS, ↑PEF (at 1 hr)	At 0.5, 1 and 48 hrs	174
Jet/ O2 at 5-6 lpm	44	4 (2-8)	Moderate-to-severe asthma	BUD	2	↑ERD (at 5 hrs); BD, Sp, HR, SS: NS	Hourly up to 5 hrs	175
Whisper Jet ³	30	10 (6-17)		BUD	0.05 mg/Kg up to 2 doses	↓ _E NO, ↑PEF, ↑SS (at 6hrs)	At 1, 3, 6 hrs	176
VentStream/PortaNeb50 or Passport Invacare ⁴	137	70	Moderate-to-severe COPD	BUD	2 qid per day	↑FEV1, ↓PCO2; AE, DO, PO2, SS, BD: NS	Every 12 hrs up to 3 days	177
LC Plus/ 6 lpm	32	4 (2-7)	Moderate asthma	BUD	2	SS, Sp, BD: NS	At 0.5, 1,2,4, 24 and 72 hrs)	178
No details ⁵	100	(6-18)	Severe asthma	FP	0.5 every 15 min up to 3 doses	↑SS; PEF, Sp: NS	At 2 hrs	179
No details	26	9 (5-13)	Asthma	BUD	1	↑PEF ; SS: NS	At 1 hr	180
PlastiMed or SunMist /DeVilbiss compressor ⁶	67	10 (6-15)	Mild-to-moderate asthma	BUD	1 every 1 hr up to 3 doses and then 1 bid	OCU, BD, PEF, FEV1: NS	Every 12 hrs up to 5 days	181
AeroFamily ²	106	64	Severe COPD	BUD	1.5 qid	↑PO2, ↓PCO2, ↑FEV1 (at 10 days); AE:NS	Every 24 hrs up to 10 days	182

*all patients were receiving bronchodilator treatment, oxygen and other required treatment as needed; BUD = budesonide; FP =Fluticasone propionate; ltp = liter per minute; bid = bis in die; qid = quarter in die; hrs =hours; min = minutes.; ↓ indicates a significant reduction for a given outcome when the active group is compared to the placebo arm; ↑ indicates a significant increase for a given outcome when the active group si compared to the placebo arm; . NS= Not significant difference between groups; Sp = Oxyhaemoglobin saturation.; PEF =Peak Expiratory Flow rate; FEV1 = Forced Expiratory Volume in one second; AE =adverse events; DO = drop-out rate; PO2 = arterial oxygen tension; PCO2 = arterial carbon dioxide tension; HR = heart rate; SS = symptom score; BD= use of rescue bronchodilator; HLS = hospital length of stay; SCU = systemic corticosteroid use; ERD = emergency room discharge rate; _ENO= exhaled nitric oxide; ¹includes 27% of children with infiltrates at chest x-Ray; ²all subjects also received (methyl)prednisolone 1 mg/Kg intramuscularly; ³not on prior stable ICS or any other corticosteroid use; ⁴on prior stable use of 1.5 mg daily beclomethasone dipropionate or equivalent; ⁵20-50% of subjects on prior stable ICS use; ⁶on prior stable use of 0.8 mg daily beclomethasone dipropionate or equivalent

ONLINE DATA SUPPLEMENT

Supplementary appendix 6. Characteristics of randomized blind parallel comparison studies including nebulized ICSs in acute asthma or COPD attacks

Nebulizer setting	Population number	Mean age (range) in years	Diagnosis	Drug treatments and daily dosage in mg	Results\$	Times of outcomes evaluation	Reference number
Hudson/ 8lpm	60	0.8 (0.1-1.5)	Asthma	BUD 0.5 every 4 hrs until discharge vs. PRE 4-6 mg/Kg at entry and 1.6-2.6 mg/kg on days 2 and 3	SS, DO, HLS: NS	Daily up to hospital discharge	173 ¹
No details	135	33 (18-69)	Severe asthma	BUD 20 vs. PRE 30 od vs. PRE 30 x4 every 6 hrs	PEF: NS	At 24 hrs	186 ²
No details	56	(1-4)	Moderate asthma	FP 1 bid vs. PRE 30 od	BD, SS ^o : NS	Every 24 hrs up to 7 days	187
No details	20	>15	Moderate asthma	FP 2 bid vs. PRE 50 od	PEF, AE, DO: NS	Every 24 hrs up to 10 days	188
Micromist/O2 at 8 lpm/ FM	80	7 (2-12)	Moderate-to-severe asthma	BUD 0.8 x 3 every 30 min vs. PRE 2 mg/Kg od	BUD>PRE for SS, Sp, HR (P<.01) and HLS (P<.001); PEF:NS	Hourly up to 6 hrs for Sp, HR, SS; daily up to hospital discharge	189
No details	46	(5-16)	Severe asthma	BUD 2 vs. PRE 2 mg/Kg up to a max of 40 mg	FEV1, PEF, SS: NS	At 24 hrs	190
No details	321	9 (4-16)	Moderate-to-severe asthma	FP 1 bid vs. PRE 2mg/kg for 4 days and then 1 mg/kg for 3 days	FP>PRE for mPEF ^o (P=.034); ePEF ^o , SS, FEV1, AE: NS	Every 24 hrs up to 7 days	191 ³
Jet nebulizer/ O2 at 5-6 lpm	71	1 (0.25-2)	Severe asthma	BUD 0.25 qid vs. 0.1 IB qid	BUD> IB for SS (P<.05) and HLS ^o (P<.01)	Every 12 hrs up to hospital discharge	192
VentStream/PortaNeb50 or Passport Invacare	133	70	Moderate-to-severe COPD	BUD 2 qid vs PRE 30 bid	PRE>BUD for PCO2; BUD>PRE for AE; FEV1 ^o , SS, PO2, DO: NS;	Every 12 hrs up to 5 days	177 ⁴
PARI LC Plus/ O2 at 6 lpm	34	4 (2-7)	Moderate asthma	BUD 2 vs. PRE 1 mg/kg	Sp, SS, BD: NS	At 0.5, 1, 2, 4, 24 and 72 hrs	178
Medel AeroFamily	106	64	Severe COPD	BUD 1.5 qid vs. PRE ⁵ 40 od	BUD>PRE for AE; DO, FEV1, Sp: NS	Every 24 hrs up to 10 days	182
DeVilbiss 646/ PulmoAide	40	11 (7-16)	Moderate-to-severe asthma	BUD 2 vs BUD 0.5 x 4 every 20 min	FEV1, SS, Sp: NS	At 20, 40, 60, 90 min	193

Legend: all patients were receiving bronchodilator treatment, oxygen and other required treatment as needed; BUD = budesonide; FP = fluticasone propionate; PRE = oral prednisolone; ICS = inhaled corticosteroid; IB = ipratropium bromide; od = once daily; bid = twice daily; qid = quater in daily; Sp = Oxyhaemoglobin saturation; m = morning; e = evening; PEF = Peak Expiratory Flow rate; FEV1 = Forced Expiratory Volume in one second; AE = adverse events; DO = drop-out rate; PO2 = Arterial oxygen tension; PCO2 = arterial carbon dioxide tension; HR = heart rate; SS = symptom score; BD = use of rescue bronchodilator; HLS = hospital length of stay; ¹includes 27% of children with infiltrates at chest x-Ray; ²on prior ICS use at daily dosage of 2mg; ³ 2% on prior stable ICSs use; ⁴ on prior stable use of 1.5 mg daily beclomethasone dipropionate; ⁵the prednisolone was administrated intravenously

List of manufacturers' nebulizer: AeroNeb and AeroDose, Nektar/Aerogen, Mountain View, Ca); LC Plus, LC Sprint, LC Star, LL, Boy, Walk Boyt, Master, ProNeb Ultra, ProNeb Turbo, PARI Pharma GmbH, Munich, Germany; Comp Air Elite (Clenny in Europe), NEU22 MicroAir, Compact XL and Elite, Omron Healthcare, Inc, Vernon Hills, Ill; SideStream, VentStream, CR60, PortaNeb, Philips/Respironics, Pittsburgh, PA; CompMist and MabisMist II, Mabis Healthcare, Inc, Lake Forest, Ill.; Lumiscope 6610, The Lumiscope Company, Inc., East Brunswick, N.J.; Acorn22, Mizer, Vital Signs, Inc, Totowa, N.J.; Aquatower, Medical Industries America, Adel, Iowa; MediMist, AvaNeb, OptiNeb and UpDraft-II, formerly Hudson Respiratory Care Incorporated, now Teleflex Medical, Research Triangle Park, NC; Novair II; VisOne, Stratos, Envoy, Invacare, Napa, Ca; AeroTech II, CIS-US, Bedford, Ma Cirrus, Intersurgical Incorporated, Liverpool, NY; 644, 646, PulmoAide, Traveler DeVilbiss Corp; Somerset, Pa.; Downdraft, Whisper and Fan Jet, Marquest, Englewood, Co.; MB-5, Nebula, Bimboneb ,MarkosMefar, Bovezzo, Italy; MistyNeb, Baxter, Valencia, Ca/Allegiance, McGaw Park, IL; NebuTech, Salter 8900, Salter Labs, Arvin, Ca; Aiolos, Aiolos Medicnsk Teknik, Karlstad, Sweden; Inspiron, Intertech Resources, Inc., Bannockburn, Ill.; Optimist, Unomedical Inc., McAllen, Tex; SPIRA, Respiratory Care Center, Hameenlinna, Finland; AERx, Essence, and Ultra, Aradigm Corporation, Hayward, Ca.; Sonik, Evit Labs, Sacramento, Ca; AeroEclipse, Trudell , London, Canada; Maxin MA-2, Clinova Medical AB, Malmö, Sweden, Multisonic, Schiller Medizintechnik GmbH, Switzerland, Medel, San Polo di Torrile, Parma, Italy